

ANNALS of SURGERY

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Symposia on
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II. BURNS

Including papers delivered before the American Surgical
Association, Cleveland, Ohio, April 6-8, 1942

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The Annals of Surgery in Spanish

WITH the simultaneous publication of this June Number of the Annals of Surgery in Buenos Aires, Argentina, by the Guillermo Kraft Company, and in Philadelphia by J. B. Lippincott Company, the journal and these two venerable publishers enter upon a new epoch in their long careers.

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The Annals of Surgery was founded by Dr. Lewis Stephen Pilcher, in 1885, to meet what he thought was the need for the first journal of its kind in the English language. It was not until the 26th Volume appeared, in July, 1897, that J. B. Lippincott Company took over its publication and continued its successful development.

The Annals began to publish the Proceedings of the New York Surgical Society in 1885, and of the Philadelphia Academy of Surgery in 1893. It became the official organ of the American Surgical Association in 1928, although since the foundation of this Association in 1880 it has published the large majority of the papers presented before it. Since 1935 it has been the official organ of the Southern Surgical Association.

In addition to the manuscripts received from these national surgical associations, the pages of the Journal have been in the past, and are at the present time, open to the publication of original contributions, controversial and original surgical subjects, and surgical research.

The policy of the journal has been formulated by a distinguished editorial board representing the medical schools and the national surgical societies of the United States and Canada. In the future this board will sincerely hope to secure the support, inspiration and privilege of consulting members from our sister republics in South America, where surgical work of such a high caliber is being performed.

In the past the journal was published only in English, in spite of the fact that it has been distributed in 35 foreign countries. Beginning with this issue it will be published in Spanish and will be distributed by the Guillermo Kraft Company. Thus wrapped in the fine raiment of the language of the immortal Cervantes, our new journal will be able to enter the hospitals and consulting rooms of Latin America as an intimate friend and surgical coworker. It will enlarge its usefulness, and bring to North Americans the advantage and privilege of a genuine understanding of feelings and ideas that only language clearly expressed can convey. To us in North America this free intercourse of ideas and feelings with our surgical colleagues of South America is an inestimable advantage from which we have been too long deprived. To our mutual good fortune, this joint enterprise of the *Annals of Surgery*, the Guillermo Kraft Company, and the J. B. Lippincott Company has turned to reality what for some time seemed only a dream difficult to attain.

Walter Estell Lee
Chairman Editorial Board

TRANSACTIONS

OF THE

AMERICAN SURGICAL ASSOCIATION

MEETING HELD IN CLEVELAND, OHIO

APRIL 6-8, 1942

ADDRESS OF THE PRESIDENT

THE DEFENSE OF THE HUMAN BODY AGAINST LIVING MAMMALIAN CELLS*

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EVERY LIVING ORGANISM depends for its survival on the possession of at least two powers: The power of adaptation and, if necessary, resistance to its external environment; and the power of maintaining stability, within certain limits, of its own internal economy. These two abilities are found in all animals from ameba to man, but apparently the problems involved grow in complexity with the increasing complexity of structure and function of the higher forms of life. This is well illustrated by the response to trauma. The cutting in half of certain of the simpler living creatures may result in each half forming a complete new survivor. Such mechanical insult to any of the adult higher animals would be invariably fatal, but note that the earliest stage of the fertilized ovum, even of man, can also apparently survive complete fission. But the response to trauma is only one of many reactions of defense against the external environment. Another great field of reaction is dependent upon the intimate presence of other living organisms or their products, and includes within its scope such conditions as infection, parasitism and intoxications. In the higher animals, and particularly in man, the psychic or emotional reaction to the environment is another manifestation of response of the greatest interest and importance. Now much fruitful study has been devoted to these and other particular forms of response-behavior in many different animals, and while, no doubt, much remains to be learned, at least the problems have been recognized, methods of attack have been devised, and many substantial results have been obtained. As much cannot be said for our knowledge of the defense mechanism against the introduction of alien living mammalian cells.

The second great power of the organism, that of regulating and controlling its internal functions, also, has many specific phases that have been the subject

* Delivered before the American Surgical Association, Cleveland, Ohio, April 6-8, 1942.

of long and intense study. Digestion, absorption, secretion, the maintenance of the circulation, the function of the nervous system, are but partial aspects of the subject that we have called general physiology. Physiology, in its classical sense, does not cover the whole field. The physical and chemical processes that regulate and maintain the composition and osmotic pressure of body fluids, the phenomena related to membranes, surfaces and molecular behavior fall within the scope of biochemistry and biophysics. The conscious and subconscious states that affect the internal activities of the body are material for the student of psychology. All of these varied and numerous functions must be coordinated and equitably controlled if the higher animal, particularly man, is to survive and prosper. To this regulated interrelationship Cannon¹ has given the name "homeostasis." His numerous writings on the subject have greatly helped to establish and popularize this concept of the living being as a mechanism dependent upon a highly complex system of internal checks and balances. Here again, a vast deal has been learned and much still remains to be learned. At any rate, methods and techniques of study, many of them intricate and highly specialized, have been evolved and successfully applied.

There is a special phase of this whole problem that has apparently lagged behind, at least so far as the interest of the medical profession and of surgeons is concerned. To be sure, the biologists have engaged themselves with it, but often the living material with which they work is so different from the human, that their results may not be transferable. I refer to the reaction of the higher animals, particularly man, to the living cells of mammals. The problem has two distinct aspects that correspond to the two properties of living creatures just now set forth, and each of them is rich in theoretical and possibly practical interest. The first concerns the reaction of human beings to implanted living mammalian cells—a defense reaction. The second concerns the control of the human being over the growth, destruction and repair of its own cells—a special phase of homeostasis. Later, a development of these two statements will be attempted. Perhaps here it may be well to glance briefly at some of the biological studies bearing on the problem.

Dr. Ross G. Harrison² has employed heteroplastic grafting extensively in his experimental studies of embryology. By this technique he has made many fundamental contributions to his chosen field, particularly the cystologic sources and relationships in the development of many structures. What concerns us here is the remarkable success of some of these grafting experiments. In the amphibia during the larval stage, not only may organs such as the eye, and whole limbs, but, indeed, large parts of one animal may be successfully grafted onto another animal. These grafts will take between individuals of different species, and some of such composite animals, called chimeras, have developed through the stage of metamorphosis into living adult forms. This tolerance for foreign tissues does not exist in the same degree, of course, for the higher animals among the vertebrates, in which respect there is a graded series, the higher forms showing increasing resistance to such alien

grafts. It has been stated that successful cross-grafts between species are limited to cold-blooded animals, and that in mammals even grafting between individuals of the same species and variety encounters great intolerance except in cases of close blood relationship.

That these statements are not universally true is evidenced by the work of Eastlick,³ who transplanted limbs between embryos of various avian species with a certain number of successful experiments that survived hatching and lived with the foreign limb also surviving. We are fortunate in having on our program to-day Doctor Willier, whose intensely interesting original work is in the same general field. Leo Loeb⁴ has done a great deal of interesting work upon the general subject of transplantation and, in 1930, published an extensive review of it. In this he records observations of many writers, in addition to his own investigations, and presents a philosophical discussion of the whole problem. He introduces a special terminology, using the expression "organism differential" to indicate the basic differences between different animals and "individuality differential" to mean the total of physical and chemical characteristics peculiar to the separate individuals of the higher animal series. These he attributes to the specific genes and chromosomes. Except perhaps for identical twins, no two higher animals are exactly alike in these endowments. There is a graded scale of increasing diversity beginning with siblings, extending through blood relatives, variety, species and genera. Because of this inherent endowment an individual possesses a chemical constitution to which cells from any other source are alien in varying degrees, and in which they provoke a reaction that leads to their destruction. He does not believe that this inherent reaction can be modified or broken down by any method yet suggested.

There has been, of course, an enormous amount of clinical work done on the general subject of grafting, and a great deal on cross-grafting. Most of this has been confined to the reporting of the introduction of various tissues into human beings, with an overwhelming incidence of failure, but without serious effort to explain or prevent the failure. Among the few publications that deal with underlying conditions affecting cross-grafts is Holman's⁵ work on protein sensitization in isoskin grafting. Holman doubts that cross-grafts of human skin are ever successful, finds that taking grafts from donors of the same blood group as the host makes little difference in the generally poor results, and attributes these results to the chemical differences between the tissues of host and graft. He thinks the grafts serve as sources of foreign protein intoxication, and lead to the development of a reaction like anaphylaxis. He further cites observations that suggest that this reaction is highly specific against the donor tissue causing it, and does not affect grafts from another donor, which, however, soon develop their own specific destructive chemical reaction.

The control of the multicellular animal over its own cells is obviously an instance of the general principle of homeostasis. However, it has received far less consideration, or, at least, efforts to study it have been far less successful

than in the case of other mechanisms of homeostasis. The movements of water, salts and proteins between the blood, the lymph, the intercellular spaces, and the cells themselves have been the subject of much study and impressive results. But who knows why the thyroid gland reaches an optimum size and then stops growing? Why do certain tissues throughout life possess the power of regeneration after injury, and other tissues have this power only in a very limited way, or only in embryonic life? What stops the regeneration of tissues when they reach the optimum stage, and prevents abnormal overgrowth? There are many such questions that we have all asked ourselves many times. They lie at the root of this problem of cellular homeostasis. The investigative attack on them has so far been very unproductive. We take refuge in speculative phraseology. We say an organ's size is conditioned by the physiologic need for it. But what mechanism implements that need, and what brakes keep it in check? Is it a balancing of hormonal stimulants? Is tissue pressure a factor? Does the metabolic product of a certain type of cell exert an inhibitory effect upon the growth of that type of cell? These things should be susceptible of investigation, if we can evolve proper technic. This matter of normal balance and restraint of cells and organs has its highly practical importance as well as its biologic interest. It concerns the healing of every wound, the response of work hypertrophy on the muscles, the development of compensations for damages done to various structures. It also, of course, is fundamental to the whole cancer problem. Every pathologic new growth represents an escape of a special tissue from the general restraints of cellular homeostasis. A great deal of study has been devoted to the discovery of carcinogenic agencies, and most valuable progress has resulted. Less attention has been given the defense mechanism against cellular overgrowth. Perhaps the problem is much harder to grapple with. At the present time, one might generalize the situation somewhat as follows: A normal cell is subject to the normal restraints on its growth and reproduction. A greatly abnormal cell, badly damaged or perverted greatly in its internal mechanism, becomes essentially a foreign cell, and hence the victim of the normal defense reaction against alien cells and is thrown off or destroyed. But a cell somewhat modified from normal by some agency—chemical action, radiation effect, or what-not—may be near enough to normal to escape the destructive reaction against alien cells, yet sufficiently diverted from normal to escape the restraining mechanism of normal cellular homeostasis. That is cancer. Should we not then concern ourselves more with these two great basic protective mechanisms which perhaps are really different phases of the same mechanism and try to discover how they work? We may learn how to sharpen the body's discrimination against damaged cells, in other words, heighten its cancer resistance, if we know the method of discrimination against alien cells. It is helpful, no doubt, to state a problem, but far more difficult to solve it, and, so far, no very promising line of attack has been developed in the study of the mechanism of cellular homeostasis. Perhaps the approach may be less arduous to an understanding of the defense of the body against alien mammalian cells.

That the human body does possess such a defense mechanism against

these cells will be generally admitted. All the evidence of clinical medicine and experimental investigation indicates this. Is this a specific property or is it merely a special aspect of the general resistance of living organisms to foreign substances? There are certain well known processes by which an animal reacts to such stimuli. An inert sterile foreign body may be encysted by fibrous tissue. An irritating foreign body, such as a chemically active substance, or living cells of the bacterial or protozoan order, may induce and be resisted by a suppurative response. Certain other chemical substances may be combated by a specific chemical response in the nature of an allergic or immunity reaction. It has not been proved that the reaction to living mammalian cells fits exactly into any of these pictures. Certain inferences, however, may be made from the known facts. The increasing complexity of structure, function, and chemical internal environment met in the ascending animal series is parallel to the increasing difficulty of cross-grafting. This increasing complexity is, no doubt, associated with more and more exact specialization and individualization of the body cells to fit them to a highly specialized environment, and a corresponding further removal from the totipotency ascribed to such cells as the ameba and the early fertilized ovum. These changes affect cross-grafting in two ways. The cells grafted from another mammal have been highly adapted to their own original environment, and hence are less well equipped to adjust themselves to changes, even of comparatively slight degree. On the other hand, the internal environment of the host animal is a highly complex affair that is provided with a mechanism to maintain itself constant, which apparently includes defenses against even slightly alien chemical substances, such as might be brought in by the grafting of foreign mammalian cells. When one recalls the size, complexity, and variety of protein molecules, for example, it is quite conceivable that certain proteins in the living mammal and in its cells may exhibit slight modifications that are specific for that one individual, and that would excite intolerance and reaction in other individuals, even of the same species. There are some observations that suggest such a possible explanation of the resistance to cross-grafting. When human skin is grafted to another person, it often seems to do well for a number of days, and then usually rapidly dissolves and disappears. This strongly suggests a defense mechanism that requires an appreciable time to develop, and that is a direct response to the stimulus of the foreign tissue. In short, it looks like the development of something like a specific immunity reaction. Such an explanation fits better than simpler reasons that might be given, such as lack of nourishment to the graft, inflammatory reaction caused by it, or incidental complications like bacterial infection. If the defense mechanism proves to be in the nature of an acquired immunologic reaction, there are many further questions that arise. Is such a reaction mediated through the circulating body fluids or is it a property of the host cells, or do both cells and fluids take part in it? Is it a local or a general response? Is it specific against the type of grafted tissue alone, or is it equally effective against all tissues of the donor animal? Is it limited to cells from the original donor, or has there been set up a reaction that will now function

promptly against the same type of cells from any donor? Most important of all, if such a defense mechanism explains the intolerance of the mammal for foreign living cells, is there any way in which the defense may be broken down or set aside? There is also a possibility that nerve relations may play some part in the question of survival of cross-grafts. Indirect evidence of this may perhaps be read into the experiments of Schotté and Butler.⁶ These experiments indicated that when a limb of certain amphibian larvae is kept denervated, the capacity for regeneration after injury is lost. Not only does the amputated extremity of such a limb fail to grow out anew, as it normally would, but regression and resorption start from the level of the amputation and proceed proximally, often bringing about complete disappearance of the limb. There is so much superficial resemblance in this process to what often happens to foreign tissue grafts in adult mammals that it stimulates suspicion that the lack of nerve supply to the implant might play a part in its failure.

Our work includes experimental studies on laboratory and clinical material. It is being carried on by a group of my associates on the Surgical Service of the Johns Hopkins Medical School—Drs. James C. Owings, George O. Gey, Kenneth Pickrell, and Douglas H. Stone, and enjoys the hearty support of Dr. Alfred Blalock, head of the department. As sufficient material is developed, detailed scientific reports will be published. The purpose of this paper is to establish the problem and to lay down certain generalizations based on our own previous work and that of many others. The first point of emphasis is the effort to understand why implants of alien cells die, rather than the development of a specific successful grafting technic, which may be hoped for as a later result. Certain conditions essential for the success of implants do concern the details of technique, however, and may be summarized as follows, from one of our earlier publications⁷: (1) Implants must be small, a few millimeters in diameter, otherwise the central portion dies before it can be vascularized. (2) The technique must be surgically sterile. (3) The bed to receive it must be near a good blood supply, but must not be too richly vascular, otherwise hematoma formation will choke the graft. (4) The bed should be of loose structure, otherwise tissue pressure will compress the graft. These points may be considered as established. Much more doubtful are two conditions that certain workers have thought to be necessary: (5) A physiologic need on the part of the host for the tissue grafted. (6) Anatomic correspondence of the bed with the site from which the graft is taken, such as thyroid grafts into the thyroid region of the host. So much for present knowledge of technical conditions.

The large experience of many zoologists permits certain conclusions of a general biologic nature: (1) Resistance to alien living cells is lowest in the lower forms of animal life and increases as one moves upward in the phylogenetic scale, this resistance being greatest in the mammalian group. (2) Resistance in any single species is lowest in the youngest forms and increases from embryo to old age. (3) Grafts are more apt to succeed the younger the donor individual, the best source being embryonic tissue. (4) The wider

HETEROPLASTIC GRAFTING

the biologic diversity of host and donor the less likely is success of grafting, the best opportunity being between identical twins.

In addition to the technical and general biologic conditions that affect the problem, there is finally the specific reaction of the recipient as related to the alien cells. At least two views have been advanced concerning the reaction of the host to the graft. One of these, on which much stress is laid by Loeb,⁴ emphasizes the more or less specific local tissue response about the graft; and the other regards the host reaction as essentially specific chemical in nature, similar to anaphylaxis or immunity. This brings us to the very kernel of the problem, and our work is far from that stage of advancement that would permit an answer as yet. However, enough has been accomplished to give us certain impressions. Thus, studies of autografts of thyroid in dogs show wide differences in grafted fragments made in the same way and at the same time. Some of these fragments are so well preserved as to look almost normal, and about them there is very little infiltration with leukocytes, lymphocytes, or other wandering cells. A short distance away, another fragment may show defective staining properties of the cells, breaking up of acini, and an accompanying active infiltration with leukocytes and particularly lymphocytes. Still another fragment may be completely hyalinized and imbedded in granulation and early scar tissue. To us it seems likely that the inflammatory reaction is not a defense against the grafts, *per se*, but merely the usual phagocytic response to damaged tissue. In other words, the cellular local reaction did not kill the grafts. Otherwise, all of them should be equally and simultaneously attacked. But some of the mechanical or technical factors, perhaps failure to establish blood supply in time, led to the death of certain fragments which are then removed by the well-recognized inflammatory local reactions. In short, we would interpret the local tissue reaction, not as a defense against living grafted cells, but as a scavenger reaction against dead cells.

There are a number of observations that have a bearing on the possibility that defense against alien grafts is in the nature of a chemical immunity in many cases. It was with this idea in mind that the writer, and his associates,⁷ some years ago, conducted a series of experiments. These consisted in growing for a considerable time fragments of the tissue to be grafted in tissue culture, on media containing the serum and plasma of the anticipated host. In this way it was hoped to adapt the grafts to their future chemical environment. Following these experiments on dogs, a number of human cross-grafts were performed in a similar manner, with apparently some definite success.⁸ Others have undertaken similar experiments with conflicting results—some successful, many not.⁹

It now appears to us, however, that a much better method is possible, and we are in process of developing it. As has been said, there have been many observations, both clinical and experimental, that alien grafts often seem healthy for a considerable time, perhaps two to three weeks, and then suddenly disintegrate. Such a phenomenon does not fit into our ideas either of an inflammatory reaction defense or of an immediately hostile chemical environment. In either, such form of resistance to the graft one would expect

a prompt and continuous destructive effect. It does suggest that the graft is the source of alien chemical substances, probably proteins that differ, perhaps not greatly, from those of the host, but sufficiently to act as antigens. In response to this stimulus, a defense mechanism is set in motion that produces antibodies, not originally present, that in time lead to the destruction of the alien cells of the graft. There are a number of experiments that suggest themselves as methods of testing the truth of this theory, and that we expect to carry out. There is also an obvious extension of our idea of adaptation of the graft to its environment that we also are planning to test. It consists in grafting a host with a given tissue and awaiting the development of the specific defense mechanism. Then we shall attempt to adapt the same tissue to the now stimulated host; in other words, to immunize the graft against the immunized host. We regret that much of this work is still only in the stage of development and that specific detailed reports must be deferred till some future time. Whether any of these experiments prove fruitful or not in leading to concrete results, the purpose of this paper will be attained if an aroused interest in the general problem develops.

Let us take a little time to consider the importance of this field and the opportunity it offers at the present. It would be an error to assume that other fields of surgical development have been exhausted; an error similar to that attributed to Paré, Billroth, Moynihan and Halsted, each of whom is said to have lamented the future of the young surgeons succeeding him, because all the great advances had already been made. Nevertheless, it is true that many fields of surgery are already extensively developed. In ablative surgery, the operative removal of offending lesions or organs, the greatest attainments have been achieved. Now that the skull and the chest are successfully invaded, not as a rare adventure, but as a routine, every-day performance, further progress would seem to be largely a matter of detail. No doubt better technique, better instruments, better preparation before operation, and better after-care will greatly improve results, but there are no remaining great anatomic areas for the expansion of ablative surgery. Reconstructive surgery in its various subdivisions—plastic, orthopedic, prosthetic—is still far from the stage of advancement that ablative surgery has reached. Here there are constant announcements of new achievements, and without doubt there still remains much opportunity for original development. But for those seeking a new frontier, a wide virgin country for exploitation, I would enlist your interest, your thinking, and your hard work in what may be called replacement surgery. As on every frontier, the going may be hard. As in every virgin territory, the clearing of the terrain may be backbreaking and heartbreaking, with delays, disappointments, hope deferred. It will call for toil and sweat, if not for blood and tears. But the promised reward is great. To take a single example, consider the possibilities, if we can overcome resistance to alien mammalian cells, in the whole group of endocrine deficiency diseases—a definite cure for parathyroid tetany, for myxedema, for Addison's disease, perhaps for diabetes, and possibly for other conditions not now understood. The replacement of entire

organs, useful and functioning, is not impossible. The vascular and ureteral hook-up of a new kidney could be accomplished, if the kidney would live after it had been implanted. These are obvious potential results of a conquest of the resistance of the human body to alien cells, and if the imagination be allowed free rein, they are but the beginning. There is no need, however, to exaggerate the results that might follow such a success. My purpose is accomplished if you give this plea the importance I think it deserves.

We hear much these days of military matters. There is a certain analogy between the methods of scientific attack and military offensive. The army feels out its opponent, finds weak spots, drives in a wedge here and a column there, develops a pincer movement, surrounds an area, and then reduces it. So in science, a lead in one field, an original idea in another, a new technique, a better instrument result in advances that stimulate each other. But in war, field tactics are not enough. One may win battles and lose the war unless there is a broad view, a general strategy. In science also, it behooves us to think at times beyond the day's work and the immediate problem, to survey the whole front and its hinterland. In such a survey, local issues will fall into their proper proportions and the larger strategic problems will emerge. One of the functions of such a body as the American Surgical Association is to act as a general board of strategy in its own field. The object of this paper is not to record a local advance, but to bring up for consideration a major problem—that of the reaction of the human body to its own and other mammalian living cells. Perhaps such a purpose today may seem visionary, but let us not forget that often in the story of mankind the visionary of to-day has proved in some distant tomorrow to have been the man of vision.

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REPORT TO THE AMERICAN SURGICAL ASSOCIATION
ON
ACTIVITIES OF THE DIVISION OF PROFESSIONAL SERVICE

UNDER THE SUPERVISION OF
THE SURGEON-GENERAL OF THE U. S. ARMY

BY
COLONEL FREDERICK RANKIN, M.C.
LEXINGTON, KY.

WHEN OUR PRESIDENT, Doctor Stone, invited me to make some remarks on the activities of the Division of Professional Service, under the Surgeon-General of the U. S. Army, it seemed wiser to commit my thoughts to writing in the interest of both brevity and accuracy.

As you know, the function of the Surgeon-General's Office is to provide adequate medical service for the Army at posts, camps and stations within and, on occasion, beyond the continental limits of the United States.

This makes for a very diversified type of medical service, extending from tactical units in the field to the general hospitals far in the rear. That all types of medical men are essential to the proper functioning of the Corps, is admittedly obvious, and the diversification of duties requires not only trained general practitioners and men just out of their intern-year but also specialists in every field of medicine and surgery. The Division of Professional Services of the Army has many activities, and the one which is of the most interest to you is the Subdivision of Surgery.

The duties of the Subdivision of Surgery may be outlined briefly as follows: (1) Coordination and supervision of professional care (surgical), which includes inquiries, complaints and investigation. (2) Advisory duties concerning equipment, training and personnel.

With the huge expansion of the armed forces, a concomitant multiplication of medical officers becomes inevitable, and if many of the problems which face the profession seem to be handled with some tardiness and delay, it should be remembered that confusion is inevitable under circumstances of an emergency in a democracy. When the training program for the present military forces was inaugurated, the Regular Army Medical Corps numbered approximately 1,210 officers. There were in addition about 1,150 National Guard Medical Officers and a Medical Reserve Corps of some 16,000 to 17,000 men who were immediately available to staff medical installations of the Army, and these were mobilized in a short time. There are now on duty between 12,000 and 13,000 medical officers and, with the increase of the Army as authorized at present, it is estimated that 24,000 medical officers will be essential to render proper service to the armed forces by the end of 1942. In addition to this, the Surgeon-General has recently made an appeal for 6,000 medical officers to supply the medical needs of the developing air force. To this

should be added the recent recommendation of the Surgeon-General for the commissioning of an additional 7,000 medical officers for our immediate needs; three in the grade of Colonel, three in the grade of Lieutenant Colonel, 300 in the grade of Major, 1,000 in the grade of Captain, and 5,647 in the grade of First Lieutenant. I stress the grades in which these men are to be commissioned to emphasize that this is a young man's war, that it is enormously more strenuous and exacting of stamina than World War I, and that for the immediate future it is necessary to commission a large number of younger officers for service with tactical units. These men will be drawn from interns who complete their service in July of this year, and from the men who are under 36 years of age and subject to the action of selective service.

While it is necessary to emphasize again that this is a young man's war, it should be pointed out that a large percentage of the volunteers for medical service, up to the present time, have been in the older-age groups, many of whom served in some capacity in the last war and who are young enough and able economically to give up practice and take active service now. Probably this is not the wisest thing under the circumstances, and it should be emphasized that the older generation's function is primarily one of taking care of the civilian population, of manning the medical schools of the country and, therefore, insuring the maximum output of medical men without a lowering of standards. It would not be amiss for these older men to bring to the attention of the younger physicians that they are needed by the armed forces rather than the older group, and that theirs is a distinct obligation to serve their country for these two reasons.

However, there are other points which I wish to make in discussing allocation of specialists in war surgery, which will be familiar to those of you who served in the last World War.

(1) You will recall that war surgery differs materially from civilian surgery, that it is not elective surgery but surgery of catastrophe.

(2) That there is no continuous flow of cases, but periods of long arduous duty followed by periods of complete absence of professional work.

(3) That the Army requires many professional duties completely foreign to a specialist whose specialty may be narrow in its scope.

If these facts can be remembered and buttressed by the knowledge that one has to do a patriotic service, albeit a distasteful one, I believe that civilian medical men will meet on a more common ground with the Regular Army personnel and find fewer reasons for irritation and criticism. Actually, surgery of all kinds will be done, and it will have to be done by younger men under unfavorable conditions, but out of this war, as out of others, will emerge some surgical principles which will be advantageous to future civil practice.

Another fact which emphasizes how much of this present action is a young man's war, is the type of warfare which is being waged. In a recent conversation with Colonel Gillespie, of the British Army, who has served in the Middle East and in Libya and, indeed, from all of the literature by such men as Jolly and Trueta, I have been greatly impressed with the necessity

of transporting the surgeon to the patient in the vast majority of cases rather than the reverse, which has been the practice in the past. The war of movement, where the favorite tactics revolve around widespread encircling types of maneuver, results in fewer casualties, perhaps, in killed and wounded, but in an enormous increase in the number of prisoners and missing. Because of the vast distances involved, it has been found necessary to insist on the greatest mobility of hospital installations in the theaters of operation, which means the increased use, therefore, of operating teams in small units, which are quickly and readily transportable. This streamlining throughout the entire pattern of modernized warfare has changed many hitherto set practices in the care of the sick and wounded in the advanced areas. Thus, with the lessons of the Allies in front of us, unquestionably, we should be quick to modify many of our now accepted beliefs in matters of medical organization.

Another point of enormous interest to you is, I am sure, the proper utilization and allocation of specialists. The Surgeon-General's Office has definitely recognized the sphere of usefulness of highly trained men in different specialty branches, and has adopted a policy of commissioning these men in grades commensurate with their age, training, and professional capacity.

As you know, it has been customary in the past to make all first appointments in the Medical Corps in the grade of First Lieutenant, save only for definite exceptions which relate to professional training, and I quote: "Captains, eligible applicants": (1) Eligible applicants between the ages of 37 and 45 will be appointed to the grade of Captain by reason of their age and general medical training and experience. Exception: Below the age of 37 the following training and experience will be considered in recommending initial appointments in the grade of Captain: (1) Certification by an American Specialty Board; (2) fellowship in the American Colleges of Surgery or Medicine; (3) membership in other recognized specialty societies or associations; (4) training equivalent to that required for examination by an American Specialty Board; and (5) other recognized training appropriate to the position for which recommended.

For the grade of Major eligible applicants are usually between the ages of 37 and 45, where vacancies exist, but men may be qualified for commission to this grade who have had the additional training and experience mentioned above.

There are obviously but few assignments in the grades of Lieutenant Colonel and Colonel, since a considerable number of men in these grades, on a Reserve Corps status, have not yet been called to duty because positions available for them commensurate with their rank are not at the present time open. This policy, I think, definitely indicates the great desire of the Surgeon-General's Office to obtain and utilize the best professional talent in a manner which will insure maximum professional efficiency to the sick and wounded of the armed forces.

Distribution of personnel and allocation of specialists are complex problems which will not, and cannot, be immediately solved to the entire satisfac-

tion of either the specialists or the Army, but I think tolerance, patience, and understanding of the difficulties of an enormous and hurried expansion should be the attitude of both the profession and the Army toward these changes of status.

In the 14 general hospitals now operated by the Medical Corps of the Army, the organization of the services is on a high plane, and the availability of additional specially trained medical men will unquestionably improve as time goes on. The general hospitals which I have visited in my short service in the Army during this war have been staffed in an extraordinarily efficient manner. I do not mean to say that they function in all specialty departments with the smoothness of a civilian hospital of long standing or those associated either with a medical school or group practice, but I have found splendidly trained men in charge of the services, and that professional work of a high character is being rendered.

In the station hospitals and smaller installations, a larger number of professional men are being utilized, and constant effort is being made to readjust professional services in order that the selectees, as well as the officer personnel of these particular posts and cantonments, may have available to them medical care comparable to that of the best civilian practice.

In short, one of the aims of the Division of Professional Service is to fit men who are properly trained into key positions and avoid, insofar as possible, the often repeated, and sometimes justifiable, criticism of putting round pegs into square holes. I can testify, unreservedly, to the wholehearted cooperation which is evidenced in the Office of the Surgeon-General, and I can assure you that there is every indication of a real desire to utilize professional men in professional capacities to a maximum extent, and of avoiding, insofar as possible, pitfalls which developed in a similar rapid expansion during World War I. It is my considered opinion that many lessons of that mobilization and subsequent periods of operation have been learned and are being applied zealously in an effort to smooth out many of World War I's unpleasant irritations and inequalities.

I am confident that medical care throughout the period of mobilization, training and active participation in the present conflict will be far superior to that rendered in the past, and that this will be the result of the hearty support of the medical profession as a whole, and such associations as this in particular.

A striking example of modern medical efficiency in war is at hand, as demonstrated in the Pearl Harbor engagement, an account of which most of you have had from Doctor Raydin and Doctor Perrin Long. Suffice it to say that here was an ideal set-up where in the first place the terrain was favorable, where the men were not in many instances clothed with heavy, dirty clothing, puttees and shoes, and where medical attention was immediately available within a few minutes of attack. In addition, the hospital facilities were accessible, transportation was ready and surgery was instituted in periods of from a half-hour up to many hours. The Chief Surgeon had anticipated the medical

requirements of an attack on the islands and had organized both in the military and civilian profession operating teams which became immediately available for service. The factors of immediate aid, rapid transportation, thorough débridement, plus the use of chemotherapy, and the treatment of shock by use of blood plasma and other mechanical means, are reflected in the brilliant results obtained following this battle. Subsequent inspection of the casualties has borne out the belief expressed by the early observers that, given adequate early care, proper treatment of shock, complete débridement, and the lavish use of sulfonamide drugs, we may expect a distinct lowering of mortality statistics, with a concomitant increase in the ultimate number restored to duty, or at least, saved from permanent disability.

Again, I should like to tell you that it would be difficult to overestimate the influence and helpfulness of many professional organizations in this present period. Surgical committees and various subcommittees of surgical and medical specialties, under the Medical Division of the National Research Council, have contributed efforts and advice which have been of inestimable advantage, and I can assure you that I have seen every inclination on the part of the Surgeon-General's Office to utilize these efforts to the fullest, and to accept professional advice when offered by such groups at its face value.

Today, there is no question that we are much further forward in this war, insofar as medical personnel and services are concerned, than we were in the middle of World War I. I have no illusions that professional services will be conducted to the complete satisfaction of everyone concerned, for the very individualism of our profession militates against that, and when such individualism collides with Army regulations it is certain that compromise is the only method whereby efficiency can be maintained.

In consequence, I would urge upon medical men everywhere the fact that tolerance and patience be a part of their credo, which must recognize certain inevitable dislocations of life and methods in such times of emergency.

It is our duty and desire to render to every American soldier adequate medical care. He deserves it and he should have it. I know that this is your promise as it is mine.

SYMPOSIUM ON ABDOMINAL SURGERY

TRANSTHORACIC RESECTION OF TUMORS OF THE STOMACH AND ESOPHAGUS*

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THE particular region of the alimentary tract with which we are concerned is that which begins in the esophagus at the junction of the base of the neck with the superior mediastinum and extends to a point several centimeters below the cardiac orifice of the stomach. An arbitrary division of this segment of the alimentary canal into three zones can be made as shown in the diagram (Fig. 1). The classical division of the esophagus has always been into thirds. It is our observation that both from the standpoint of the site of occurrence, and from the point of view of surgical management, it is more useful to divide it into fourths. The second and third fourths are to be thought of as the middle half.

Zone 1 extends from the base of the neck to the superior surface of the aortic arch. Removal of a growth situated in this portion of the esophagus (an uncommon location, fortunately) is a specialized problem, the management of which is not yet clear. The proximal esophageal end is so short that the establishment of an external fistula may be impracticable. The highest practical level for division of the esophagus with the construction of a suitable cervical esophagostomy is just above the superior surface of the aortic arch. If cut there, the proximal end when brought out in the neck will lie 1 or 2 cm. above the level of the clavicle. At this point the epiglottis can easily be felt by digital palpation down the lumen, and because the epiglottis is so near, a rubber tube can be worn only with great difficulty or not at all. Furthermore, a stoma located above the clavicle adds greatly to the technical difficulty of constructing an external esophagus by skin plastic procedures.

Zone 2 may be said to embrace the middle one-half of the thoracic esophagus, that portion extending from just above the aortic arch to a point just below the level of the inferior pulmonary veins. Growths in this region make it necessary to divide the esophagus at too high a level to allow the performance of an esophagogastric anastomosis. The only operation for carcinoma in this region is a partial esophagectomy which makes it necessary to bring the proximal end of the esophagus to the surface in the upper part of the chest by pulling it out through a cervical incision. Feeding is carried out by artificial means through the exteriorized lower end of the esophagus or through a gastrostomy, or eventually by swallowing through a rubber tube connection between these, or finally through a skin-plastic tube constructed to bridge the gap between the stomata.

* Read before the American Surgical Association, Cleveland, Ohio, April 6-8, 1942.

Zone 3 includes the lower one-quarter of the thoracic esophagus, the cardiac orifice of the stomach, and the adjacent few centimeters of the stomach including the fundus. Lesions located in this area are low enough to make it possible to perform an anastomosis between the esophagus and a portion of the stomach. Certain high gastric carcinomata involving a portion of the esophagus, which if approached through an abdominal incision will be inoperable, can be successfully removed through the transthoracic route. Resection with esophagogastric anastomosis is an extremely useful operation in certain cases for both esophageal and gastric carcinomata.

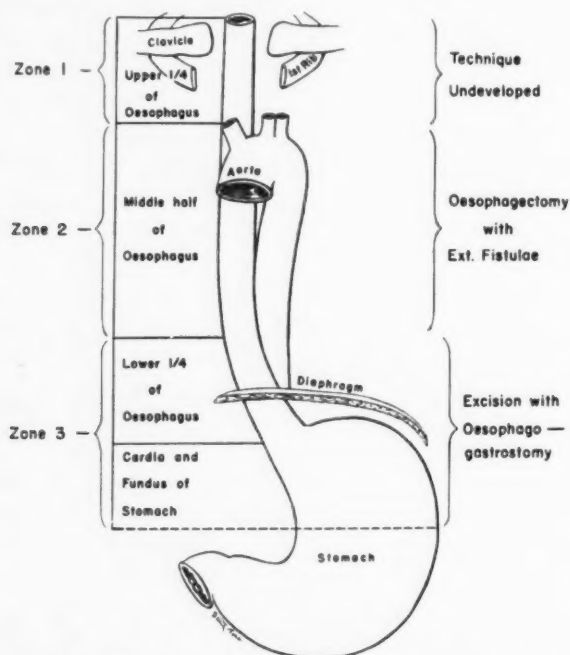


FIG. 1.—The arbitrary division of the thoracic portion of the esophagus and the cardiac region of the stomach into zones so as to facilitate the understanding of the technical problems involved in the surgical management of carcinoma arising in these several areas.

Pathologic Considerations

(1) The majority of carcinomata of the esophagus are epidermoid in character. The change from squamous to columnar epithelium usually becomes obvious at the cardia, but in certain cases mucosa of the gastric type may be found in the lower esophagus. This appears to explain the rare case of an adenocarcinoma confined entirely to the esophagus. Case 7 of this series is an example.

(2) Carcinoma arising in the esophagus often spreads in the submucous and muscular coats of the organ for a distance of several centimeters in such a way that it can be detected only by microscopic examination. This was observed in several of the cases. A noteworthy example is that in Case 3

where at a plastic operation done in preparation for the making of an external esophagus, definite microscopic extension of the tumor in the lower esophageal stoma was found in a section removed for examination.

(3) A third fact concerning the pathologic behavior of carcinoma of the esophagus is the great frequency of metastases to the lymph nodes below the diaphragm. The lymphatic drainage from the esophagus, though not thoroughly understood, may be assumed to follow in a general way the course of the vascular supply. In the upper portion the blood supply is from the inferior thyroid artery. Here the cervical nodes tend to become involved. From the level of the aortic arch down there is an increasing tendency for metastases to occur to the nodes in the region of the left gastric vessels. An analysis of the cases of carcinoma of the thoracic esophagus which came to autopsy in the 43-year period 1897 through 1940, reveals the fact that of 24 cases of carcinoma in the upper third only one showed metastases to nodes below the diaphragm. In 32 cases where the growth involved the middle third, 11 showed metastases to the subdiaphragmatic nodes. Finally, of 16 lower third growths, eight showed positive nodes below the diaphragm (Table I).

TABLE I
METASTASES TO SUBDIAPHRAGMATIC LYMPH NODES IN 72 PATIENTS WITH CARCINOMA
OF THE THORACIC ESOPHAGUS*

	No. of Cases	No. with Metastases
Carcinoma of upper third.....	24	1
Carcinoma of middle third.....	32	11
Carcinoma of lower third.....	16	8

* From the autopsy records at the Massachusetts General Hospital, 1897 through 1940.

A knowledge of this fact is, of course, of great importance in deciding about the probable curability of these cases. It may well be considered unjustifiable to subject a patient who already has metastases to these distant nodes to the mutilating procedure of esophagectomy when the likelihood of cure must be so slight. On the other hand, the striking palliative results of resection with establishment of an esophagogastric anastomosis gives a wide latitude to this operation even in the presence of distant metastases.

(4) Metastases to the liver in cases of carcinoma of the esophagus occur very late in the disease.

(5) Metastases to the lung should always be looked for because the venous return from the high gastric and esophageal areas enters the caval system directly instead of passing first through the portal system.

Determination of Operability

Exclusive of the usual considerations relative to the age and general condition of the patient, certain observations and diagnostic procedures are important.

(1) *Clinical Observations:* (a) A constant boring pain in the interscapular region of the back is often an indication that carcinoma of the esophagus has reached an inoperable stage.

(b) Persistent fever is usually an indication of inoperability in carcinoma of the esophagus or cardiac end of the stomach. It occurs as a result of infection in a deeply eroding or ulcerated growth.

(c) Rectal examination when the growth is primarily in the stomach may reveal a rectal shelf of peritoneal implants.

(d) Supraclavicular lymph node involvement is less common than was anticipated.

(2) *Endoscopic Findings:* (a) Esophagoscopy is essential to determine the nature and level of the lesion and especially to procure tissue for microscopic diagnosis. But endoscopy cannot give information concerning the degree of extension of the growth in the layers below the mucous membrane.

(b) Gastroscopy has been of limited value in lesions of the fundus of the stomach as it is difficult to see the primary growth. In five cases of carcinoma of the cardia or fundus, the growth was visualized through the gastroscope in only two cases. In the remaining three cases it was not seen.

(c) peritoneoscopy as an aid in the determination of operability proved of no value in the six cases in which it was performed. In an occasional case of widespread abdominal metastases or liver involvement, a peritoneoscopy may save the patient a major exploration. When widespread metastases have not occurred, peritoneoscopy is of no value because it is impossible to see the retroperitoneal nodes in the region of the left gastric vessels or even the lesion itself.

(3) *Roentgenologic Examination:* Roentgenologic visualization by a radiologist especially interested and skilled in the technic of examining the esophagus has been found to be of the greatest value in localizing the lesion and in predicting the degree of extension of the growth. Everything considered, the roentgenologic examination has been of more value than any other diagnostic procedure.

Preoperative Preparation of the Patient

Adequate time is taken to bring the patient's general condition to its optimal point. Oral sepsis is eradicated if possible before any serious gastric or esophageal operation is undertaken. A high vitamin, high protein, high carbohydrate diet is administered. Transfusions sufficient in number to restore the blood to a relatively normal level are important. Preoperative artificial pneumothorax is not necessary or advisable.

An intravenous infusion of glucose and saline is started immediately before the operation is begun.

MANAGEMENT OF CARCINOMA OF THE MIDDLE PORTION OF THE THORACIC ESOPHAGUS (ZONE 2)

A malignant lesion in this portion of the esophagus makes it necessary to resect at so high a level that an esophagogastric anastomosis is impossible even if the stomach is mobilized by cutting the vasa brevia, the left gastroepiploic, and the left gastric arteries. The highest anastomosis in this series was done at the level of the aortic arch. Elevation of the stomach to this

height was facilitated by a preexisting hiatus hernia. Usually it is impossible to carry out an anastomosis without a dangerous degree of tension if the stomach is elevated above the level of the inferior pulmonary vein. Anyone who has had the experience of dividing the esophagus is familiar with the extraordinary degree of retraction which takes place.

When the thoracic esophagus is to be completely resected and a cervical esophagostomy established, it is necessary to provide an enterostomy for feeding. There are several advantages which accrue from considering enterostomy as the first step in the surgical program. The enterostomy may be (a) temporary in the form of a jejunostomy if it is planned ultimately to bring the lower end of the esophagus down from the mediastinum and use it as the gastric stoma; or (b) permanent in the form of a gastrostomy which is suitable for use in plastic reconstructive procedures.

The procedure for surgical removal of a carcinoma in the mid-esophagus must be divided into two or more stages which may be grouped as follows:

First Phase of the Operation

A muscle-splitting incision is made in the upper portion of the left rectus muscle. The liver is palpated. A careful investigation of the lymph nodes in the region of the left gastric vessels is then carried out. Enlarged nodes are removed for frozen section biopsy. Of 23 cases of carcinoma of the thoracic esophagus explored in this manner since January 1940, 12 have been found to have metastases in these nodes. A palliative gastrostomy may then be carried out and the surgical program closed. If there are no liver or lymph node metastases which cannot be removed with reasonable hope of arrest of the disease, the first stage is completed by the establishment of a jejunostomy or gastrostomy, depending upon the plan for completion of the operative procedure.

A jejunostomy is performed if it is planned to use the short segment of the esophagus just above the cardia for the permanent lower stoma. This requires a second celiotomy following the esophagectomy. A lower stoma made from the stump of the esophagus has certain merits, but also serious drawbacks. There is a rapid and kind union of the stratified esophageal mucous membrane with the skin of the abdominal wall which minimizes troublesome fistula formation during the construction of a skin-tube esophagus. On the other hand, the stoma tends to be small and a delay in the passage of food from the skin-tube to the stomach has been observed at this point in one case (Case 1). We have abandoned the use of the esophagus for the lower stoma, however, for a more serious reason. The extension of cancer in the submucosal lymphatics to some distance from the palpable or visible growth has been pointed out. Preservation of any portion of the lower esophagus for reconstructive procedures may lead to the disaster of inadequate cancer surgery. A recurrence in the stoma is recorded in one patient (Case 3).

We now recommend a Beck-Jianu gastrostomy at the time of the ab-

dominal exploration. The lower stoma of the gastric tube can be brought several inches above the costal margin on the anterior thoracic wall. By taking care to construct the tube with a large diameter this type of stoma is ideal to receive the lower end of a rubber connecting tube. It is satisfactory also for the construction of an external esophagus from the skin. Experiences with this aspect of the problem are exemplified in Cases 5 and 7. The technic of the Beck-Jianu gastrostomy has been described elsewhere¹ (Fig. 2).



FIG. 2.—The stomata after esophagectomy for carcinoma of the midportion of the thoracic esophagus. Upper stoma is esophagus. Lower stoma is the end of a Beck-Jianu gastrostomy.

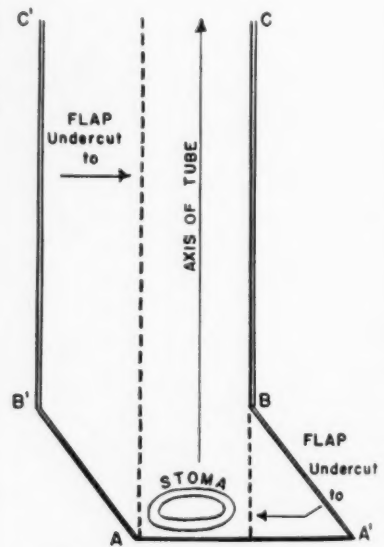


FIG. 3.—A convenient method for constructing skin-lined tube esophagus around stoma. Suture A' to A, B' to B, and C' to C. Tube can be stopped with open end at any point without leaving denuded area. This can best be visualized by cutting pattern as outlined above and folding on dotted lines.

Second Phase of the Operation

After the patient has recovered well from the preliminary abdominal operation, the growth is removed by a transpleural esophagectomy. Whether the approach should be right-sided or left-sided is debatable. That a growth located opposite the aortic arch can be reached more easily from the right side must be granted. But when working through the left side the aortic arch can be retracted sufficiently well to obtain direct access to a growth in this area by dividing the upper intercostal arteries. This is mentioned by Torek in his original article.² If the right side is used, it is necessary to do a preliminary mobilization of the esophagus in the neck as a separate stage before attempting the esophagectomy. If the left-side approach is used, the cervical portion of the operation can be done at the time of the resection, thus avoiding a separate procedure. Better access to the upper end can be had

from the left side. The determining consideration that leads us to recommend that esophagectomy be done through the left pleural cavity is the greater ease of access to the lower three inches of the esophagus. The fact that cancer infiltrates the muscular wall of the esophagus for a considerable distance away from the obvious growth makes it imperative to divide the organ as far away from the tumor as possible. Added to this, the frequency of lymph node metastases below the diaphragm as mentioned above (12 out of 23 cases) makes it advisable to open the diaphragm, divide the stomach just distal to the cardia, and excise the lymph nodes in the region of the left gastric vessels. By this procedure the entire organ with the majority of its regional lymph nodes is resected—an established principle of cancer surgery.

A description of the technic of this stage of the operation is as follows:

Technic of Operation

With the patient lying on his right side, a long oblique incision is made across the left side of the chest over the course of the seventh or eighth rib, resecting the rib from the costal cartilage to its articulation with the transverse process of the vertebra. Adjacent ribs may be divided near their necks by excision of short segments to afford the desired exposure. The pleura is incised and the anesthetist reduces the endotracheal pressure to allow the lung to collapse. If the lung is adherent it is freed enough to be retracted medially. Large gauze pads are used to protect the wound edges and a rib spreader is inserted.

With the lung retracted medially the mediastinal pleura over the esophagus is incised from the diaphragm to the aortic arch. By blunt dissection the esophagus is mobilized and a tape passed around it for retraction. As the esophagus is further mobilized the esophageal branches of the aorta are ligated and divided. One or two small branches from the left bronchial vessels must be divided. The esophagus is cut across as low as possible and the distal end is inverted with silk sutures. In the complete operation the esophageal hiatus of the diaphragm is enlarged by dividing muscle fibers and the cardia delivered into the thorax. The esophagus is divided at the cardia and the defect in the stomach wall closed. After removal of the esophagogastric cluster of lymph nodes the diaphragm is sutured. A finger cot or small sheet of rubber is tied over the cut end of the esophagus.

The mediastinal pleura above the aortic arch is incised at a point posterior to the left subclavian artery. The esophagus is mobilized by dissection at this point and another tape passed around it. By working now from above, now from below the aortic arch, that portion of the esophagus which lies behind it is liberated. If necessary, better access to this portion may be obtained by dividing one or two of the upper intercostal arteries to allow retraction of the aortic arch forward and to the left, away from the esophagus. In order to free the esophagus completely, the vagus nerves are separated from it, but if one or both are inseparably adherent to the growth, they are divided. The esophagus is then pulled up from behind the aortic arch.

The next step is to make a small incision in the lower portion of the neck

along the anterior border of the sternomastoid muscle. The dissection is carried down to the prevertebral fascia, retracting the carotid sheath laterally. It may be necessary to ligate and divide the lateral thyroid vein. The attachments of the esophagus in the base of the neck are freed by dissection with the finger from above and below, creating a passageway from the thorax to the neck. A rapid alternative way to complete this step is to mobilize the esophagus in the lower portion of the neck by blunt dissection with the finger from within the thorax. A short cervical skin incision made by an assistant then gives ready access to the passageway thus created from below. A tape on the end of the esophagus is passed up from the chest and out the cervical incision and the esophagus is delivered in its entirety. If a bulky friable growth is present, it may be desirable to divide the esophagus above it rather than attempt to force the entire organ through the cervical tunnel. The upper end is then delivered into the neck and the lower esophagus, including the growth, removed through the chest incision.

Interrupted silk sutures close the mediastinal pleura. A layer-by-layer closure of the chest incision is made by interrupted silk sutures, taking care that the lung is fully reexpanded before the chest is made air-tight. Sulfanilamide crystals may be spread over the pleural surfaces and mediastinum before closure. Drainage is not used.

After the dressing has been applied to the thoracic incision, the patient is turned on his back for the completion of the operation as follows: The growth-bearing portion of the esophagus is removed with ample margin, taking care to cut across the viable portion of the esophagus which at that level is determined by the blood supply of branches from the inferior thyroid arteries. Taking note of the remaining length of the proximal end, a short transverse incision is made through the skin of the upper thorax, below the clavicle if possible, and the end of the esophagus is drawn down through a subcutaneous tunnel and out through this incision. A few fine silk sutures are loosely applied to anchor it. The cervical incision is then closed. The positive pressure within the trachea must not be released before the neck incision is closed because there is a direct communication through the neck and superior mediastinum with the left hemithorax. At the end of the operation examination is made for residual pneumothorax on both sides. Large collections of air are removed by aspiration.

Care of the Patient after Esophagectomy.—The patient is kept in an oxygen tent during the first 24 to 72 hours or until it is obvious that there is no embarrassment of respiration due to pneumothorax or the accumulation of fluid within the chest. A small effusion need not be removed, but aspiration may be necessary if it is large. After 24 hours, small feedings are started through the gastrostomy and regular gastrostomy feedings are resumed as rapidly as the condition of the patient will allow.

The upper esophageal stoma may be allowed to empty into a large dressing of gauze which is changed frequently. As an alternative, a rubber tube is fastened into the end of the esophagus. In one case the pressure of the inner end of the tube produced a small area of necrosis and a fistula through the

wall of the esophagus near the stoma resulted. A troublesome local cellulitis developed. After ten or 12 days a soft rubber tube may be used to connect the esophageal stoma above and the Beck-Jianu gastrostomy opening below. In low-lying growths the proximal end can be left long enough so that the stoma will reach below the clavicle. In such cases a rubber tube connection serves very well. On the other hand, if the growth is high (opposite the aortic arch or above, the proximal end will be so short that it will come only to the surface of the neck above the clavicle where it is exceedingly difficult to apply a rubber tube because of the proximity of the epiglottis, the motions of the neck, and the angle of the esophagus with the skin. Furthermore, a rigid, angulated tube of glass cannot be made to fit well or to stay in place easily.

Patients are surprisingly comfortable, considering the mutilation to which they have been subjected, and recovery is usually rapid. On the average they are able to be out of bed by the tenth or twelfth day after operation.

Subsequent Course.—Following the esophagectomy, the patient may be allowed to return home wearing a rubber tube between the stomata. Through this, liquid food can be ingested, and in one notable case (Case 3) the patient ate soft solids and ground meat, washing them down with draughts of fluid. As a rule patients gain weight and strength. But they are not a happy group as a whole. They often fret at their inability to eat a normal solid diet and complain of the annoyance of the daily care of the rubber tube. It would seem from the humane standpoint, therefore, that one should look forward in every case toward the completion of an external esophagus by some type of plastic procedure.

Third Phase of the Operation

Many methods have been proposed for the construction of an external esophagus from skin, stomach, colon, or jejunum. Usually the skin of the anterior thoracic wall can be used successfully, but the details of the problem vary from case to case. The construction of a skin tube is more easily accomplished in women than in men. In men the skin is tighter and less



FIG. 4.—Case 6: The completed external esophagus. The prominence opposite the lower portion is caused by the fundus of the stomach.

freely movable. Furthermore, in many cases there is too much hair to make it advisable to turn in the skin most readily available. In one such patient it was estimated by counting the number per square inch that there were 1,500 coarse hairs growing in the rectangular area of skin which would have been required for the tube between the stomata. In this case (Case 5), with the help of Dr. Bradford Cannon, a tube of skin with a pedicle at each end has been constructed from the right side of the chest in the midaxillary line where there is no hair. This tube is to be transplanted and eventually connected to the two stomata.



FIG. 5.—Case 6: The completed external esophagus filled with barium taken by mouth.

In two cases a functioning extra-thoracic esophagus has been completed by turning in a tube of skin (Cases 1 and 6). In the first of these (Case 1), the lower stump of esophagus was used as the stoma in the epigastric region. In the second case (Case 6), the upper half of the stomach with a short end of esophagus attached was brought up over the anterior chest wall through a subcutaneous channel. By this means the lower esophageal orifice was brought up to the level of the nipple and a shorter skin tube was required. The functional result in the latter case has been slightly better than in the former.

In a fourth case, using a Beck-Jianu gastrostomy stoma for the lower end, a skin tube esophagus was almost completed (one stage only lacking) when the patient died of pneumonia (Case 7).

The case histories may be consulted for certain details of these plastic procedures.

Summary of Experience with Surgical Treatment of Carcinoma of the Midportion of the Thoracic Esophagus (Zone 2)

From February, 1940 to February, 1942, 21 patients with carcinoma of the midthoracic esophagus have been considered possibly suitable for resection (Chart 1). In all of these a preliminary exploratory celiotomy was performed. Twelve of these patients were excluded as candidates for esophagectomy because of the presence of lymph node metastases below the diaphragm. Of the nine cases without positive nodes below the diaphragm, one died of pneumonia before the chest could be explored. Eight patients of this group of 21 came to thoracic exploration. Of these, two were found to have a locally inoperable growth and resection was abandoned. Resection was

carried out in six cases. Of these, one died postoperatively of a cerebral accident.

Of the five patients who survived the esophagectomy, one has since died of distant metastases, and one died of pneumonia during the process of making an extrathoracic esophagus. Of the three ultimate survivors, one is living and well with a completed external esophagus, another is so content with his

Fate of 21 Patients with Carcinoma of the Mid Portion
of the Thoracic Esophagus Selected from a Larger
Group as being Probably Favorable for Resection:
February, 1940 to February, 1942

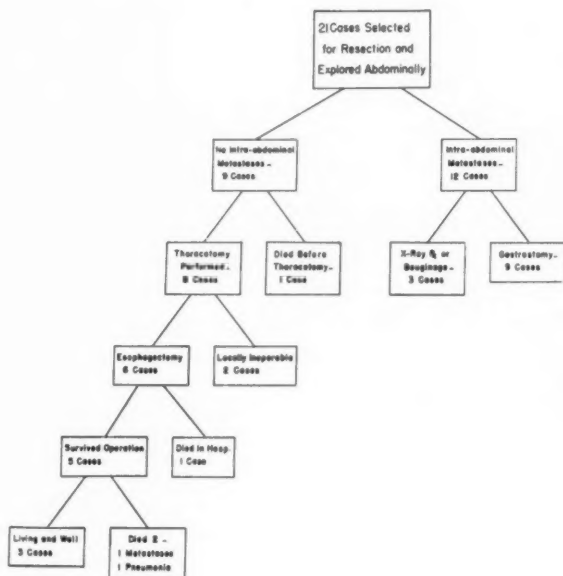


CHART I.

rubber tube connection that he has thus far refused to consent to the making of a skin tube, and the third is in the process of having an antethoracic skin tube esophagus constructed.

TABLE II

CASES OF CARCINOMA OF THE MIDPORTION OF THE THORACIC ESOPHAGUS (ZONE 2)

Name	Date	Age	Operation	Result
E. P.	1938	43	Esophagectomy	Alive with metastases. External esophagus completed
E. C.	1939	63	Esophagectomy	Died postoperatively
R. B.	1940	48	Esophagectomy	Died with recurrence
C. W.	1940	53	Esophagectomy	Died with recurrence
A. M.	1940	59	Esophagectomy	Well. External esophagus partially completed
J. L.	1940	48	Esophagectomy	Well. External esophagus completed
P. L.	1941	57	Esophagectomy	Died 4 mos. after operation
J. G.	1941	72	Esophagectomy	Well
B. L.	1942	68	Esophagectomy	Died postoperatively

Table II shows the total group of nine cases of carcinoma of the mid-thoracic esophagus in which an esophagectomy was performed, including the three cases done before February, 1940. These three were not mentioned in

the above analysis because of lack of investigation of the abdominal lymph nodes at the preliminary abdominal operation.

MANAGEMENT OF CARCINOMA OF THE LOWER ONE-FOURTH OF THE THORACIC
ESOPHAGUS AND CARDIAC END OF THE STOMACH (ZONE 3)

A growth located in or near the cardiac orifice of the stomach, if operable at all, can be resected and an anastomosis made between the proximal end of the esophagus and the stomach. This operation utilizes a transthoracic approach through the diaphragm and is employed for certain low esophageal and high gastric carcinomata; in other words, for any growth in Zone 3 as defined above. A carcinoma of the cardiac orifice of the stomach usually involves grossly or microscopically, the lower end of the esophagus, so that resection with a margin of safety is a technical impossibility if the conventional abdominal incision is employed. The technical advantages of the approach through the chest include greater ease of access to all of the structures involved in the procedure, the possibility of removing a longer segment of esophagus, and the avoidance of a total gastrectomy in the high gastric cancer group.

In comparison with the abdominal approach to this region, data collected by the Anesthesia Service indicate a more stable maintenance of vasomotor equilibrium even though the actual operation may be of longer duration. It is also our impression that postoperative pain and pulmonary complications are lessened. Certainly they are no greater.

Preoperative Preparation

In addition to the usual preparation of the patient the following procedures may be mentioned:

(1) A Levin tube is inserted intranasally on the morning of operation. The end of this is kept at a level just proximal to the growth, and during the course of the operation constant suction is applied. This tube is then left in place above the level of the anastomosis during the first few days of convalescence.

(2) It will be obvious to anyone familiar with the technic of modern thoracic surgery that the induction of artificial pneumothorax as a preliminary to operation is unnecessary and undesirable.

(3) In depleted patients, starved by their inability to swallow, the performance of a preliminary jejunostomy may be advisable. If the state of nutrition is reasonably good, it is unnecessary. Of the 11 patients upon whom a resection with an esophagogastric anastomosis was performed, a preliminary jejunostomy was considered necessary in three. Seven cases in this series were successfully done without a jejunostomy.

Technic of Operation

The patient is placed on his right side with his left arm drawn upward. A long oblique incision is made over the course of the ninth rib (Fig. 6). The latissimus dorsi, trapezius, and a few fibers of the serratus anterior

muscles and a part of the lumbodorsal fascia are of necessity divided. The incision may be carried through the eighth or ninth intercostal space or through the periosteal bed of the resected ninth rib, according to individual preference. The intercostal incision can be made more rapidly, but is more difficult to close unless one relies entirely on large pericostal sutures. The rib resection technic requires more time with the opening, but provides an easier and more accurate closure. The incision must be long and the rib is

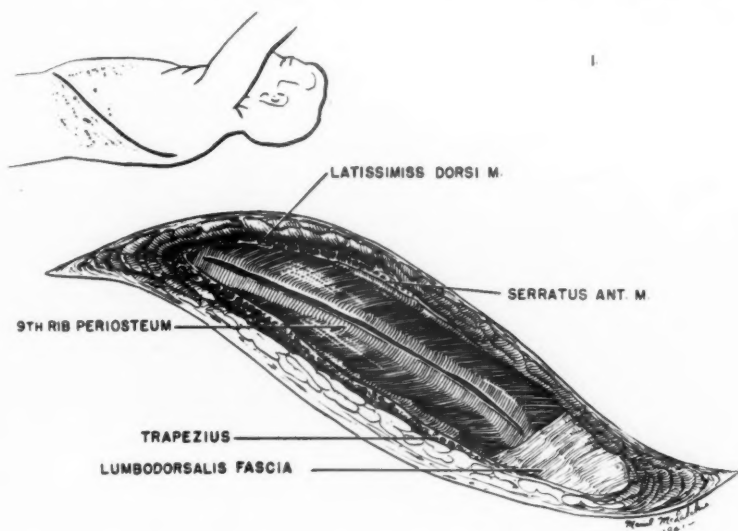


FIG. 6.—Transthoracic approach to the stomach—details and location of incision.

resected from the cartilage to its articulation with the transverse process. In order to gain more exposure adjacent ribs may be divided posteriorly. It is well to avoid resecting or dividing the tenth rib, upon which the stability of the lower part of the thoracic cage depends. The necessity for cutting the costochondral arch is the chief objection to the combined abdominothoracic incision. Special rib retractors may be used if available, but two Balfour self-retaining abdominal retractors, one in each end of the wound, will serve very well. Although they have been omitted in the illustrations, large gauze pads are used to protect the wound edges.

The anatomy of the field of operation will be appreciated from a study of Figure 7. If the lung is adherent, it is separated by sharp dissection. After retracting the lung, the phrenic nerve is injected with novocain to immobilize the diaphragm. If resection is carried out, the phrenic nerve is crushed to maintain the immobility of the diaphragm during the postoperative period.

An incision is made through the diaphragm extending from its costal attachments to the esophageal hiatus. If a resection is decided upon, the incision is extended to divide the hiatus. In doing this the left inferior phrenic vessels on the undersurface of the diaphragm are ligated and divided.

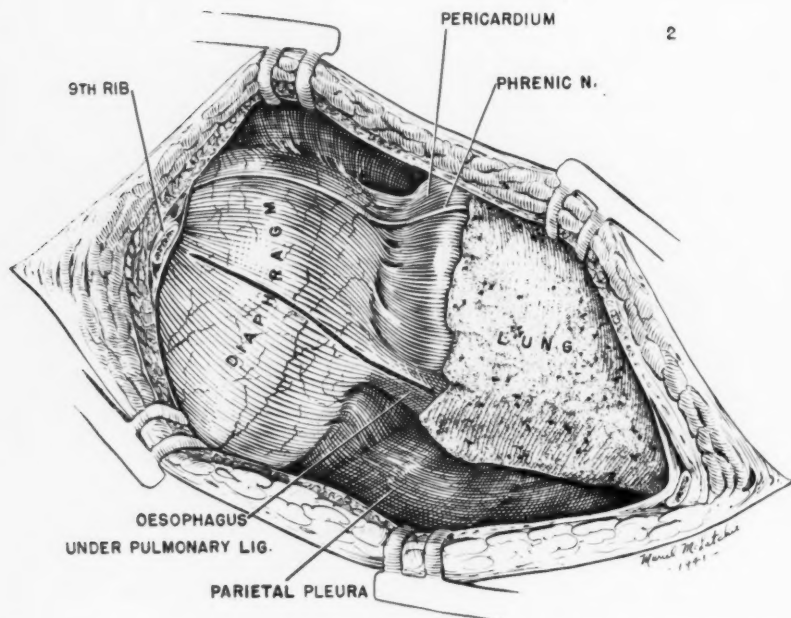


FIG. 7.—Transthoracic approach to the stomach—anatomy of the field of operation before incision of the diaphragm.

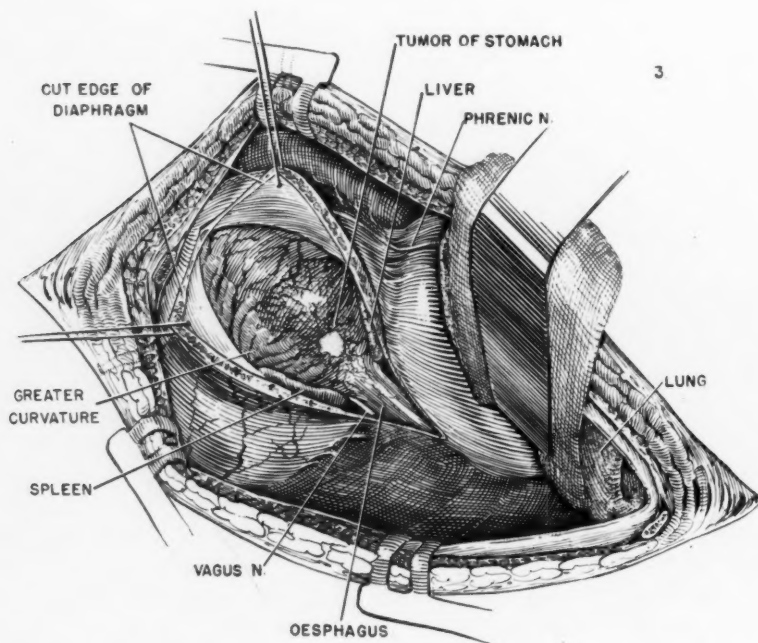


FIG. 8.—Transthoracic approach to the stomach—anatomy of the field of operation after incision of the diaphragm.

It is at this point that one begins to realize the superiority of the trans-thoracic approach over that through the abdomen. The tumor, the anterior and posterior surfaces of the stomach, the retrogastric space, the retroperitoneal lymph nodes, and those in the upper portions of the gastrocolic and gastrohepatic ligaments are directly accessible. Palpation of the liver is easily performed and in every case it has been possible to explore with the hand the entire abdomen, including the pelvic cavity, to feel for metastases.

If a resection can be performed, the phrenic nerve is crushed and the incision through the diaphragm completed. Long traction-sutures passed through the cut edges of the diaphragm and brought out through the wound are useful (Fig. 8). The spleen is held out of the way with a gauze pack. The liver is held back with a long flat retractor. The pulmonary ligament is incised and the lower two or three inches of esophagus mobilized.

The fundus and cardiac end of the stomach are mobilized by dividing the left gastric vessels and the vasa brevia. Vessels passing behind the cardia and the lower esophagus to anastomose with the inferior phrenic vessels are divided. Division of the vasa brevia and liberation of the upper pole of the spleen from extension of the growth into the lienorenal ligament is readily accomplished. Close adhesion of the upper pole of the spleen to the growth is an indication for its removal without attempting separation.

The left gastric artery may be divided at its origin in order to remove the regional nodes which surround it. The splenic artery is isolated at the point of its emergence on the upper border of the tail of the pancreas, and the posterior peritoneal wall of the lesser omental cavity at this point excised if the growth lies adjacent. Extension of the carcinoma to surround the splenic artery at this point may require its resection followed by splenectomy. Further extension to the tail of the pancreas is managed by partial resection of this organ.

At this point the field of operation is protected with a second set of gauze pads and care is taken to cover the intra-abdominal and intrathoracic surfaces as completely as possible. Whatever method is used to minimize contamination from the lumen of the esophagus, care is taken not to crush or devitalize it. A rubber-covered clamp may be applied loosely; a lung hilum tourniquet fitted with a broad tape may be used; or if suction by the indwelling tube is effective, no occluding device whatsoever need be applied. The esophagus is divided well above the highest level of visible or palpable tumor, but always at least two or three inches above the cardiac orifice.

Because of the strictly segmental distribution of its blood supply, the mobilization of the lower esophagus is done gently to avoid damage to the esophageal arteries which arise from the aorta. The esophagus is divided at least two or three inches above the cardia because the interruption of the left gastric, the vasa brevia, and the inferior phrenic arteries, all of which contribute to the blood supply to its lower extremity, may deprive the segment just above the cardia of an adequate circulation.

The stomach is divided below the level of the growth, placing the clamp

so that as much as possible of the greater curvature is preserved. The stump of the stomach is completely closed by suture. An end-to-side anastomosis between the esophagus and stomach is then performed (Fig. 9).

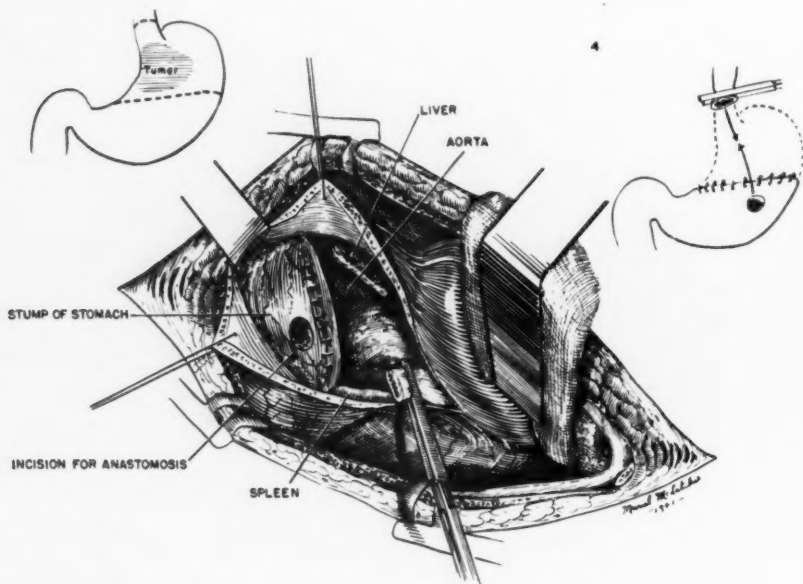


FIG. 9.—Transthoracic approach to the stomach—appearance after removal of the growth and closure of the cut end of the remaining portion of the stomach; preparation for the anastomosis.

Certain differences between this anastomosis and other gastro-intestinal anastomoses are important in determining the details of technic. Not only the tensile strength but the water-tight quality of the anastomosis depends on the row of sutures in the mucous membrane. This layer is sutured with the care and nicety accorded the placement of a vermilion border suture in the lip in the most meticulous plastic operation. Interrupted sutures of fine silk are used throughout.

To avoid any clouding of the field with blood while placing sutures in the mucous membrane, it has been found advantageous first to complete the preparation of the gastric part of the stoma. This is done before the stomach is anchored in position for the actual anastomosis. Certain authors report that a stricture is likely to result if a linear incision in the stomach is used. This objection is said to be overcome by excising a circular button from the stomach wall in forming the stoma. Both methods have been employed in our cases without discernible difference.

The sequence of the subsequent steps in performing the anastomosis is a detail which may be altered according to individual preference or the presenting complexities of regional anatomy. These steps are recorded in the classical sequence of gastro-intestinal anastomosis.

After complete hemostasis has been secured in the gastric incision made

for the anastomosis, the stomach is anchored high on the posterior thoracic wall to relieve tension on the suture line. Interrupted mattress sutures unite the posterior muscular layer of the esophagus to the serosa and muscles of

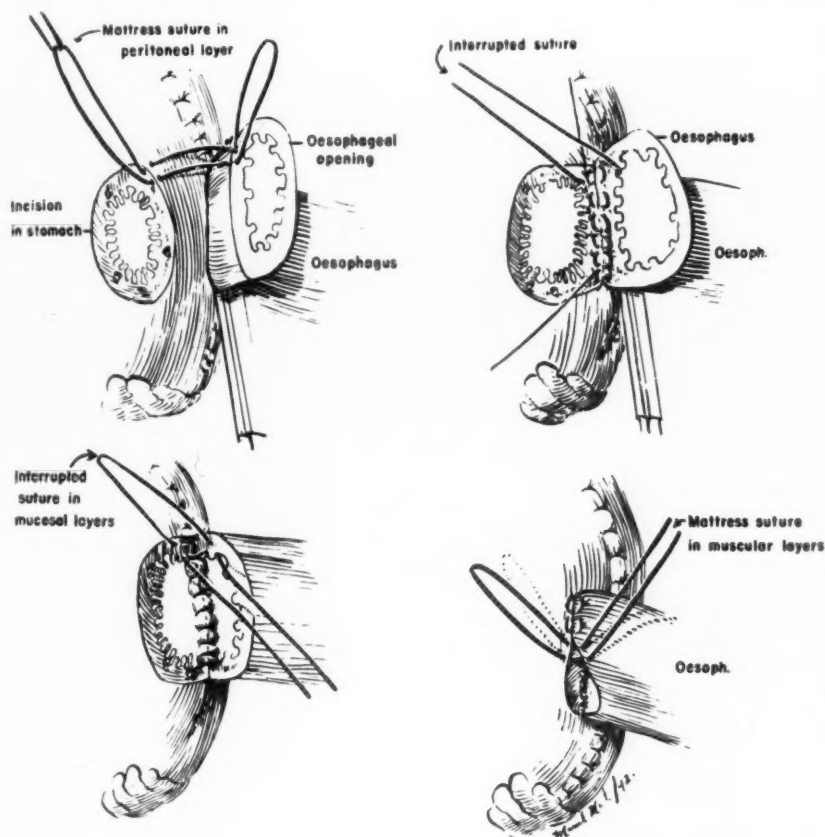


FIG. 10.—Transthoracic approach to the stomach—details of the esophagogastric anastomosis.

the stomach. The mucous membranes are approximated with sutures so placed that the knot lies within the lumen. These are tied without tension which will lead to cutting when the tissues swell. An anterior row of sutures completes the union of the muscular coat to the stomach. The suture line is covered with omentum (Fig. 10).

Certain measures are employed to make certain that the suture line is relieved from any tension. The leaves of the pulmonary ligament and adjacent mediastinal pleura are sutured to the stomach close to the suture line. The cut edges of the diaphragm are sutured to the stomach wall several centimeters below the level of the anastomosis. The remainder of the diaphragmatic incision is then closed. The thoracic wall incision is closed in layers (Fig. 11).

During the course of the operation the left lung is kept partially collapsed,

but it is important at intervals of 15 to 20 minutes to allow the anesthetist to expand the lung fully for a few moments. At the completion of the operation, while the first layer of pleural sutures is being inserted, the anesthetist begins to expand the lung again, and before the last suture of the first layer is tied, the surgeon makes certain that expansion is complete.

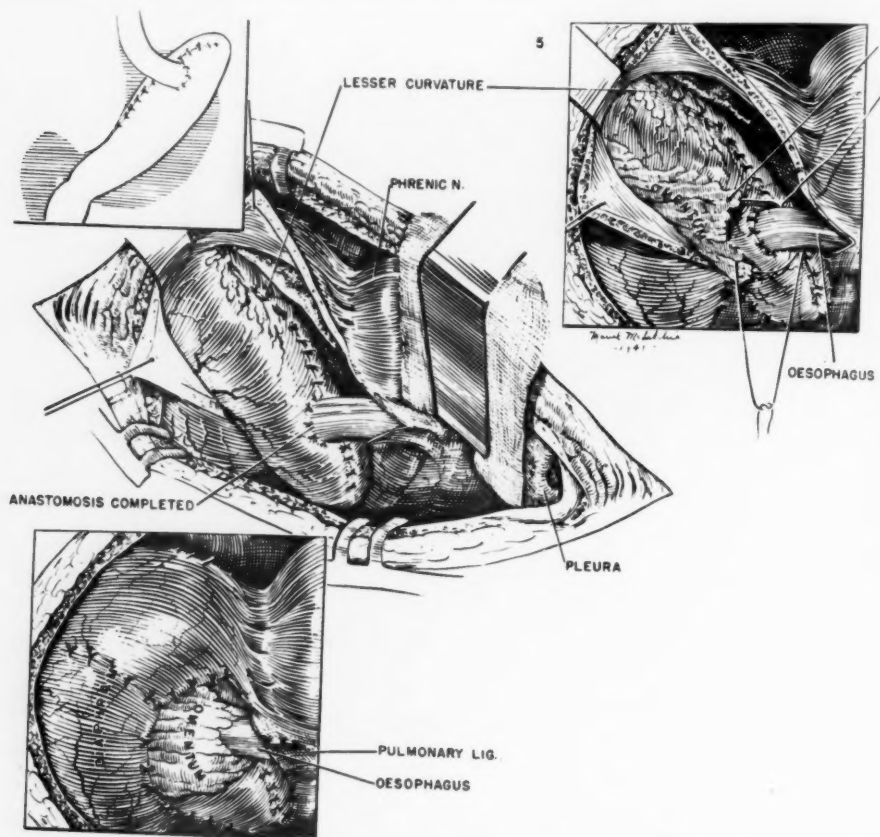


FIG. 11.—Transthoracic approach to the stomach—completion of esophagogastric anastomosis. Inserts show details of fastening omentum around the suture line and the methods of fixation of the stomach to avoid tension, suture to the chest wall, the leaves of the pulmonary ligament, and the paralyzed diaphragm.

Postoperative Care

Except for the incision and the conduct of the anesthesia, the operation itself differs little from any abdominal operation. The after-care, however, is practically entirely a thoracic problem, except for the usual considerations attendant upon the management of a gastric anastomosis. The patient is immediately placed in an oxygen tent or hood. Special nurses are essential. The usual transfusion and parenteral fluids are given. Suction is maintained on the intranasal catheter. This will usually drain a bloody fluid at first, but later, during the first few days, several hundred cubic centimeters of bile and gastric secretions may be aspirated. The lower end of this tube is kept

at a point just above the anastomosis. Fluids by mouth may be started in a week. The nasal tube is then removed. A soft solid diet is given by the end of two weeks.

Postoperative Complications

(1) Auricular flutter occurred in two cases. One of these (Case 16) recovered; the other (Case 13) died on the fifth postoperative day.

(2) Three patients developed empyema (excluding the two fatal total gastrectomy cases, both of which died because of sepsis). These were Cases 2, 5 and 14. In one of these (Case 2) the complication was serious and developed because of leakage from the anastomosis which was done by the now discarded method of implantation of the end of the esophagus into the stomach. The others were of minor importance and responded promptly to drainage.

Physiologic Considerations

(1) *Action of the Diaphragm:* (a) In those cases where only an exploration is possible, preservation of the function of the diaphragm is undoubtedly preferable. In the cases with resection an inactive diaphragm is believed to be advisable to prevent pull on the sutures of the anastomosis. In this series no ill effects attributed to the paralyzed diaphragm were observed.

(b) Herniation through the diaphragm has been a complication in experimental animals, and in dogs has been a cause of vomiting. It can be successfully operated upon, as was shown by Adams and associates.³ There are apparently no reports of its occurrence in man.

(c) Pain referred along the course of the phrenic nerve to the left shoulder has not been observed even in the inoperable cases where the nerve has been preserved.

(2) *Gastro-intestinal Motility and Digestive Function:* The possible harmful effects of dividing the vagus nerves must be considered. In some of the dogs described by Adams and associates, although they survived the operation, a slow death from inanition occurred which was attributed to loss of the vagus function. One of the patients in this series developed a severe nutritional deficiency characterized by all the signs characteristic of vitamin B-complex deficiency and nutritional edema. This occurred in spite of feedings by jejunostomy, parenteral administration of vitamin concentrates and liver extract, and transfusions. Although there was a complicating empyema, the nutritional deficiency appeared to have contributed in a large measure to the patient's death about three months after the operation. This has not occurred, however, in any of the other patients who have had a resection and esophagogastrostomy nor in two others on whom an esophagectomy for carcinoma was performed, at which time both vagi were cut. These patients maintain a good state of nutrition.

Fluoroscopic observation of the stomach after this operation reveals a diminished or absent gastric motility, but that of the duodenum and jejunum seems to be approximately normal. As would be expected also, there is

spasm of the pyloric sphincter. Careful anatomic studies, published by G. A. G. Mitchell,⁴ would lead one to expect an overactivity (or rather an unopposed action) of the sympathetic nerve fibers that remain in the region of the pylorus and lower portion of the stomach.

Careful fluoroscopic observation of one of these patients (Case 6) whose lower esophageal stump and the fundus of the stomach were brought over the lower ribs and out through a subcutaneous tract, confirmed these expectations. In this case the gastric peristalsis was so weak and the pyloric sphincter so overactive that it was necessary to perform a pyloroplasty by the Hienke-Mikulicz technic so as to inactivate and widen the pyloric sphincter. The details of a study of this case are to be published elsewhere.

As a result of this disturbance of gastric motility and hypertonicity of the pylorus, several of the patients upon whom an esophagogastric anastomosis has been performed complain of more or less difficulty of an obstructive nature for a few weeks after operation. This often leads them to believe that they are unable to swallow and may mislead their medical attendants to believe that they have an early recurrence. Fluoroscopic observation demonstrates that the delay is at the pylorus, not at the anastomosis. Experience has shown, however, that the condition is usually temporary and will correct itself.

A few patients complain of regurgitation of gastric contents into the esophagus, especially when lying flat. It has been relieved by elevation of the head of the bed or the use of more pillows.

TABLE III

TRANSTHORACIC APPROACH TO THE STOMACH (21 CASES)

Resection Followed by Esophagogastronomy (11 Cases)

Case	Name	Age	Diagnosis	Result
(1)	H. E.	59	Carcinoma of cardia	Well 26 mos. after operation
(2)	A. P.	59	Carcinoma of fundus	Died 3 mos. after operation
(3)	J. T.	55	Carcinoma of fundus	Died, with recurrence 14 mos. after operation
(5)	P. B.	68	Carcinoma of cardia and fundus	Well 16 mos. after operation
(9)	A. D.	67	Carcinoma of lower esophagus	Well 14 mos. after operation
(11)	W. E.	49	Carcinoma of cardia and fundus	Well 11 mos. after operation
(13)	O. R.	52	Carcinoma of cardia	Died in hospital
(14)	S. M.	44	Carcinoma of lower esophagus	Well 7 mos. after operation
(15)	A. K.	64	Carcinoma of cardia	Well 7 mos. after operation
(16)	J. L.	49	Carcinoma of cardia	Well 6 mos. after operation
(19)	H. C.	50	Carcinoma of lower esophagus	Well 3 mos. after operation

Total Gastrectomy with Esophagojejunostomy (2 Cases)

(10)	M. O.	55	Carcinoma of entire stomach	Died in hospital
(17)	G. W.	46	Carcinoma of cardia	Died in hospital

Total Gastrectomy in Two Stages (Inoperable at Second Stage) (1 Case)

(12)	W. A.	43	Carcinoma of entire stomach	Discharged from hospital
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Local Excision of Tumor (2 Cases)

(6)	E. L.	50	Sarcoma of fundus	Well 13 mos. after operation
(21)	M. S.	36	Neurofibroma of cardia	Well 2 mos. after operation

Exploration Only (5 Cases)

(4)	C. W.	40	Carcinoma of fundus	Discharged from hospital
(7)	F. S.	62	Carcinoma of fundus	Discharged from hospital
(8)	J. O.	72	Negative stomach	Discharged from hospital
(18)	L. G.	51	Carcinoma of fundus	Died in hospital
(20)	C. E.	36	Carcinoma of cardia and lower esophagus	Discharged from hospital

Summary of Experience with Carcinoma and Other Neoplastic Lesions of the Cardia and Lower Esophagus (Zone 3)

Table III shows that a total of 21 patients with lesions in this area were explored by the transthoracic route. Of these in one case no tumor was found. In four cases of carcinoma of the cardiac end of the stomach the growth was found to be inoperable. One of these remained in the hospital for terminal care and died four weeks after the operation. The other three were discharged two to three weeks after exploration. In a sixth case a two-stage transthoracic total gastrectomy was attempted, but the lesion was found to be inoperable at the second stage. There were two cases, one of neurofibroma and the other of fibrosarcoma of the fundus of the stomach, treated by local excision of the tumor through the transthoracic route. In the remaining 13 cases of carcinoma a resection was done. In two of these a total gastrectomy with an esophagojejunal anastomosis in the thorax was done. Both died, one because of leakage at the suture line, the other of widespread sepsis from soiling at operation but with an intact suture line. In the remaining 11 cases a resection and esophagogastric anastomosis was performed. In three of these cases the growth was in the lower end of the esophagus; in eight it arose in the stomach. There was one postoperative death (from auricular flutter). Ten patients survived the operation. Two of these have died of recurrent disease. All of the remainder are well and free from symptoms from three months to two and one-half years after the operation. These results may be said to compare favorably with those from resections for carcinoma in other locations in the stomach.

Note: Case histories to accompany this paper will be published in the October issue of ANNALS OF SURGERY.

REFERENCES

The extensive literature on the subject, as well as personal communications from many surgeons, has been freely utilized in attempting to resolve the maze of technical details that form the subject of this communication. Rather than to risk error by ascribing a source for specific ideas, we prefer to present the material as a recital of personal experience, completely disclaiming any originality of concept or methods.

- ¹ Sweet, R. H.: Gastrostomy in Cases of Carcinoma of the Esophagus. *Surg., Gynec., and Obstet.*, **73**, 55-62, 1941.
- ² Torek, F.: The First Successful Resection of the Thoracic Portion of the Esophagus. *J.A.M.A.*, **60**, 1533, 1913.
- ³ Adams, W. E., Escudero, L., Aronsohn, H. G., and Shaw, M. M.: Resection of the Thoracic Esophagus; Experimental and Clinical Study. *Jour. Thoracic Surg.*, **7**, 605-620, 1938.
- ⁴ Mitchell, G. A. G.: Nerve Supply of Gastro-Esophageal Junction. *Brit. Jour. Surg.*, **26**, 333-345, 1938.

DISCUSSION.—DR. DALLAS B. PHEMISTER (Chicago): These results of Doctor Sweet's and Doctor Churchill's are perhaps the best that have been reported, and the series is large enough, in itself, to establish transthoracic resection as the best treatment for tumors in these locations.

I have had 12 cases in which resection was performed, with eight immediate survivals. In 12 cases, the carcinoma was in the middle one-half of the esophagus, and the

tumor was removed through the left chest and neck. Four cases survived the operation. One died, after four or five days, of infection. Two cases subsequently died of the recurrences. Two are still free from recurrence, one, for over three months, and one, for 16 months.

In seven cases, the carcinoma was located lower down, three, in the esophagus, and four, in the proximal stomach. Resection was performed, followed by anastomosis.

Four cases survived the immediate operation. One died of leakage and infection at the end of a week, one, of fibrillation and heart failure, and one, of pneumonia and mediastinitis, without leakage.

Three cases are alive and apparently free from recurrence, one for nine months, one for 14 months, and one for four and one-quarter years. The last case was reported by Doctor Adams and myself, it the longest survival that I can find. This patient had carcinoma of the lower esophagus, with metastases in the lymph nodes, in the upper portion of the lesser curvature, and it demonstrates that metastases in this region are not necessarily a contraindication to operation.

The 12 cases have been operated upon in one stage, with one exception, where a preliminary gastrostomy was performed. I believe that the routine should be a one-stage operation through the left chest. In the stomach cases, when the resection is extensive, there may be difficulty of approximation for anastomosis. In one such case I incised the peritoneum alongside the duodenum and mobilized it so that anastomosis then became possible.

As to the technic in the highest esophageal cases, where anastomosis is impossible. The left chest and the upper abdomen are prepared and draped in the same field. If the esophageal tumor, after opening the chest, appears to be resectable, the lymph nodes of the upper part of the lesser curvature are then explored for metastases and the possibility of their operative removal; in one such case we found them involved and removed them. The esophagus is then freed in its entire extent and divided below the level of the tumor. If the lower end of the esophagus is long enough, the stomach is mobilized in its upper portion, a stab incision is made below and to the left of the xiphoid, and the esophageal stump is then pulled through. That procedure can be carried out very quickly. It has been employed in three cases.

If the stump is too short, a large mushroom catheter may be inserted, transthoracically, into the stomach and pulled through an anterior stab incision. The chest is then closed, the neck is draped, and the esophagus brought out through a neck incision, after which the tumor is resected and the esophagostomy established either through a lower incision or, if it is too short, through the same incision.

The thoracic duct was involved by the tumor in two cases, once within the abdomen and once up near the thoracic arch. It was ligated, divided, resected, and there was no leakage of lymph afterward. The left lobe of the liver was attached to the tumor in one case, and it was resected.

I want to show some malleable retractors for use in these resections. (Slide.) This is for the lower resections when anastomosis is made. It is roughly a cross-section of the chest at that level. (Slide.) Here is a malleable retractor for resection higher up. We have two or three for use, according to the level of the tumor.

DR. WALTMAN WALTERS (Rochester, Minn.): I should like to make a few comments on one case of this type which I have done, paying tribute to Doctor Phemister and his associate, Doctor Adams, and to Doctor Ochsner and Doctor DeBakey, for their excellent description of the technic of the operation.

I regret to say that I am not a thoracic surgeon, and that is one of the reasons I am reporting this case, in view of the fact that, as a general surgeon the transthoracic removal of a carcinoma of the upper part of the esophagus did not seem to be such a difficult procedure.

I will not go into the details of the case, except to say that I followed exactly, as best I could, the description which Doctor Ochsner and Doctor DeBakey described in their summary of their results in cases of this type. I believe that I learned a great deal from the case. For example, in Doctor Churchill's and Doctor Sweet's drawings, you will remember that the lower part of the esophagus seemed to be on a curve at its entrance to the anterior wall of the stomach. I believe that in the ensuing dilatations of the anastomoses which were necessary in the case I did, if you do not have that curve but

have a direct line between the esophagus and the anterior wall of the stomach, it will be much easier to carry out the dilatations.

Secondly, I believe that Doctor Ochsner's use of the upper part of the stomach—that is, the greater curvature—as an anchor, so to speak, as well as a tab, to protect the posterior part of the anastomosis and relieve the tension on it, is a very valuable procedure. I do not think it was illustrated in Doctor Churchill's and Doctor Sweet's drawings, but possibly they employed the same method. It relieves the tension on the anastomosis and then, with the use of the omentum around it anteriorly, it is very helpful in contributing to the blood supply of this area.

Finally, I believe that, at least in my very limited experience, the skill of the anesthetist contributed to this patient's survival of a long operative procedure. You will recall, I said it was not difficult, but most certainly it was long. It took two hours and one-half to complete this procedure, and, at the suggestion of the anesthetist, every few minutes we would allow him to inflate the lung, cyclopropane being used. Then the loss of heat was prevented as well as one could possibly do so, with the use of moist gauze dressings. Multiple transfusions were used in this case, both preceding the operation and afterward. A one-stage jejunostomy was performed at the first operation. I did not know enough to ligate the gastrohepatic omentum or the ligamentum gastrolieale and its blood vessels at the time of the preliminary operation, which probably would have made the mobilization of the stomach much easier. But I was trying to feel my way along and failed to do it. Yet I found, in the second stage, that it had not particularly made the operation more difficult. In other words, I am only presenting this case because it may give encouragement to some of the surgeons who are less experienced in intrathoracic surgery and physiology.

DR. ALTON OCHSNER (New Orleans, La.): A few words about the technical details. I am one of the advocates of the right-sided approach, primarily, because I think it is easier to do, and also because I have recently been able to demonstrate that one can remove all of the distal portion of the esophagus. I am talking about those cases in the resection of the mid-portion of the esophagus.

At the last meeting of the American Society for Thoracic Surgery, held in Toronto last June, the criticism was brought up that from the right side one could not remove enough of the distal portion of the esophagus. Since that meeting, I have had an opportunity to explore one of the patients upon whom we had operated from the right side. In reconstructing the esophagus anterior to the thorax, we brought up the stomach and found the entire esophagus had been removed, and only the fundus of the stomach was left. So I think that it is possible to remove all of the esophagus from the right side.

Another technical point is that, in contradistinction to what Doctor Phemister does, we feel that the tumor should be removed in the chest and that it should not be brought up through the neck because of the danger of a possible implant from the tumor.

A word about the combined abdominothoracic tumor—those tumors located lower down. We feel that they should be undertaken in two stages, in contradistinction to the midportion of the esophagus—at the first stage not only determining whether the case is operable or not, but freely mobilizing the stomach, as Doctor Walters has mentioned.

In one of our patients the tumor had extended down to the lesser curvature. The case seemed inoperable. We mobilized all the gastrohepatic omentum, freed it down the greater curvature for about half the distance, and were able to remove all of the lesser curvature. That patient is alive now, two years later. Had it not been for the fact that we had mobilized the stomach before, I am sure that it would not have been possible to have accomplished as radical a resection as we were able to perform.

DR. EDWARD D. CHURCHILL (Boston, Mass., closing): I hope that the members of the Association will be willing to reserve their judgment in this field until those who are working in it have had a longer chance to solve some of these difficult problems. I think that it is a maze of conflicting details at the moment.

I think there are two or three fundamental principles that we must keep in mind in approaching any one individual patient. First of all, our goal is the cure of cancer, and we know, from bitter experience in other fields, that any concessions made to future reconstructive plastic procedures may be pitfalls.

Second, we are doing our best to avoid intolerable mutilation under the excuse of palliation. I think the figures that Doctor Sweet showed were that approximately 50

per cent of the patients with the midportion of the thoracic esophagus involved, which seem operable thoracically, have extensive abdominal lymph node metastases, and in those cases, rather than subject them to the mutilating procedure, we "call it a day" and quit.

In the technical details, there is no limit to the points of controversy and discussion. I should emphasize what Doctor Sweet said about the suture line in the esophageal gastric anastomosis, which is on a different principle than the suture line of the gastro-enterostomy because the water-tight suture line and nearly all of the tensile strength of that suture line depend on accurate mucous membrane approximation, and those mucous membrane sutures are placed with the exactitude and with the degree of tension that we would use in the fine plastic procedure on the lip. There must be no tension, and there must be accuracy.

Doctor Ochsner and Doctor Sweet are on different sides in regard to the method of approach. While Doctor Ochsner points out that the entire esophagus can be removed from the right thorax, I wonder if he would also say that the left gastric artery can be ligated at its point of origin and resected with the lymph nodes that run between that point and the cardiac end of the stomach.

I do not agree with Doctor Ochsner's comment that, preceding abdominal operation, it is necessary to mobilize the stomach when you are contemplating performing an esophagogastric anastomosis, because we find that the exposure through the diaphragm is adequate to carry out a complete total gastrectomy, should the occasion necessitate.

I will also point out that the surgeon may approach a patient, expecting to do a resection, with an esophageal gastric anastomosis, and that he will find, by the time that he has gone far enough down on the stomach to give him a safe margin and far enough up on the esophagus to give him a safe margin, he cannot bring the two ends together, and he must convert his procedure to the "turn-out" operation.

DR. RICHARD H. SWEET (closing): There are just one or two notes I made during the discussion that I would like to point out. As Doctor Churchill said, in two cases we have converted a planned esophageal gastric anastomosis into a "turn-out" operation and have done essentially Doctor Phemister's one-stage operation.

I am sorry to hear Doctor Walters say that these cases should be undertaken only by thoracic surgeons. Or did I make the wrong inference? I think they should be done by abdominal surgeons, because, although I am told that many thoracic surgeons are excellent abdominal surgeons, I know that the abdominal surgeons can make a most satisfactory anastomosis, and I think the anastomosis is the most important part of the operation.

We have had no strictures in our cases. Just why, I do not know, but it remains as a fact. Perhaps we have paid unusual attention to the detail of the anastomosis.

THE PROBLEM OF INTESTINAL GASES COMPLICATING ABDOMINAL SURGERY*

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TO THE EXPERIENCED SURGEON gaseous distention before or following abdominal surgery is an unwelcome sign and so often indicates a serious condition it cannot be regarded lightly. At the same time a flat abdomen during convalescence is extremely comforting. Fortunately at this time, with better knowledge of its etiology, this complication is often preventable. Only those who practiced surgery 20 years ago, when gas formation was too little understood, can appreciate the importance of experimental physiologic studies of intestinal gases, and their origin, to the safety of abdominal surgery. To appreciate the serious problem of gaseous distention and the erroneous conception concerning its cause, and the methods employed for its relief, the younger surgeon should read the older text books,¹ which devote many pages under the headings of "Postoperative intestinal distention," "Acute postoperative intestinal obstruction," "Acute postoperative gastric dilatation," "Preoperative purgation, postoperative purgatives," "Mouth laxatives or mild purgatives" (such as calomel and soda), "Medicated rectal enemata." Turpentine stupes, poultices, icebags, strychnine, physostigmine and atropine were commonly used. Each surgeon had his especial enema containing various drugs. One famous surgeon of the South had an enema of renown which was called "16 to 1 enema" after the W. J. Bryan money-standard-plan of 16 parts of silver to one of gold. This enema had 16 drugs to one part of water, and no gas could resist it.

The erroneous belief that intestinal gases were the result of putrefaction caused preoperative purgation and starvation to be practiced, routinely, to prevent postoperative distention. It was a long time before it was realized that such practices, far from preventing distention, actually increased and prolonged distention and delayed the return of peristalsis. Furthermore, the resulting disturbance of water and electrolytic balance was at times so great as to bring about death of the patient. Although it was early noticed by some workers that cases which were operated upon as emergencies without preoperative preparation, had less distention than those who were extensively prepared in advance, nevertheless, there seems to have been no implication that the purging and starvation policies were actually at fault.

What are the Effects of Gaseous Distention? Gatch² has stated that: "Distention is the most important cause of death from all forms of bowel obstruction, mechanical or paralytic, and most of the other supposed and suggested causes of death cannot exist in the absence of distention." With this statement we agree. Since distention does play such a vital rôle in

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abdominal surgery, it might be well to consider first of all the specific effects which it produces.

Effects of Gaseous Distention—Toxic Effects: There is very little support for the theory, largely originated by Amussat,³ that with accumulation of gases and liquid material in the intestines toxic products are absorbed into the general circulation. Some workers contend that liquid or gaseous contents of the bowel or other harmful products as undigested protein and bacterial toxins are absorbed, but these are not under normal conditions absorbed until they are broken down into nontoxic material.^{4, 5}

Effects of Impairment of Circulation of Bowel Wall from Gas Pressure: Gatch, following extensive investigation, is of the opinion that the various effects of gaseous distention may be largely traced to the pressure upon the bowel wall, affecting its blood and lymphatic circulation. This pressure results in anemia of the bowel wall and, later, a congestion, which may seriously involve the viability of the wall. In addition, normal lymphatic capillary function may be seriously involved, with the loss of the selective power of absorption: "(1) By diminishing the volume of blood flow through the intestinal wall; (2) by altering the physical forces involved in absorption; and (3) by damage to the intestinal wall; this affects both the activity of the mucosa and the physical forces which hinder or promote absorption."*

Effect of Distention on Intestinal Tone: Not among the least important of the effects of distention is the interference with the normal motility of the bowel. With stretching of the tissue, decreased activity of the nerve mechanism of the bowel, as well as of the muscular contraction, results; and if the distention lasts for a considerable length of time, even though the distention is relieved, the power of contraction is delayed, often for several days, resulting in what is known as "paralytic ileus." Abnormal distention of all hollow organs, if prolonged, results in atony. This is commonly seen with the urinary bladder. Again, sudden overdistention of the stomach may result in "acute dilatation" with a loss of contracting power. The over-distended intestine behaves in a similar manner. Also the temporary ileus which accompanies trauma to the bowel will be prolonged if the bowel is distended but if the bowel remains collapsed normal peristalsis is sooner restored. If this is true, keeping the bowel free of gas is indicated after trauma to the bowel (operation).

Other Effects of Distention Less Easily Explained may be: (1) *Changes in blood concentration* have been reported by Fine and coworkers, and also Gatch and Battersby, who observed that intraperitoneal loss of blood protein results from distention, and blood concentration follows. (2) *The effect of distention on liver and kidney function* has been indicated by Orr, and associates.⁶ They think that distention may play a part in the failure of liver and kidney function: "Liver function is first impaired by nerve reflex inhibition due to distention of the intestine. The anoxemia present in cases of severe intestinal distention may produce a marked impairment in the formation of bile and urine."

* Personal communication.

Van Duyn II⁷ has concluded from careful clinical observation that abdominal distention may be the etiologic factor in blood changes similar to "leukocytic exhaustion." He found a mixed degenerative-regenerative picture with neutrophils, myelocytes, monocytopenia and absence of eosinophils. He states: "Abdominal distention is concluded to be at least one important cause of the degenerative blood picture. The actual mechanism of production is through absorption from the distended intestinal wall of some apparently nonbacterial toxic substance which acts either directly or indirectly as an inhibition of leukopoieses."

ORIGIN OF INTESTINAL GASES

In order to prevent gaseous distention it is necessary to understand the origin of intestinal gases.

Air as the Chief Source: The origin of intestinal gases has been generally misunderstood for a long time, and the belief that intestinal gases originate within the bowel and are largely the result of putrefaction is firmly fixed in many minds. Kantor⁸ said, in 1918, after animal experimentation, that: "In general, gaseous accumulations in the upper digestive tract have atmospheric air as the base. The air is introduced by swallowing." Again, Bickman,⁹ in 1924, wrote that postoperative distention was partly due to swallowed air.

In spite of these early observations, surgeons have been slow to appreciate and accept the fact that swallowed air is by far the chief source of intestinal gases in normal intestines as well as the intestine in a condition of ileus or obstruction.

In support of the theory that swallowed air is the chief source of intestinal gases, analyses of these gases have frequently been made, and the variations from the gases of the air have been found to be slight. An analysis of the gases of the air is as follows:

	Oxygen (O ₂)	Nitrogen (N ₂)	Carbon Dioxide (CO ₂)	Methane Hydrogen
Composition of air	20.96%	79%	.04%	—

TABLE I

ANALYSES OF INTESTINAL GASES IN ANIMALS WITH ILEAL OBSTRUCTION

Singleton and Rogers

Analyses of Gases Withdrawn from Intestine of Mechanically Obstructed Dogs

Dog No.	Hours	CO ₂ %	O%	N%	CH ₄ %
1	72	4.5	10.7	83.0	1.8
2	48	10.7	3.1	82.6	3.6
6	12	5.9	13.1	80.8	0.2
7	48	9.1	1.5	89.4	0.0
8	48	9.3	0.0	90.7	0.0
9	72	14.0	5.8	77.4	2.8
10	72	12.1	0.8	87.1	0.0

Average Composition Intestinal

Gas	9.51	5.0	84.42	1.2
Composition of Atmospheric Air	0.04	20.94	79.02	0.0

Wangenstein's¹⁰ Report

N	Carbon Dioxide	O ₂	Methane Hydrogen	H ₂ S	Ammoniated Methane
70%	6-12% (near that found in blood gases)	10-12% (drop after 72 hours)	Low %	1-14% (increase after death)	½-4% (increased with long obstruction)

Wangensteen says: "In quantitative determination of the origin of gases occurring in small bowel obstruction, about 68 per cent of the gas was estimated to have arisen from swallowed air. The amount formed within the body was 32 per cent of the amount, 70 per cent originated from diffusion from the blood into the bowel lumen, and the remaining 30 per cent arose from decomposition of food matter." In other words, only 9 per cent of the total was from decomposed matter.

Clinical Analysis of Intestinal Gas: McIver, Benedict and Cline¹¹ analyzed gases drawn from the rectum in postoperative distended patients and nonsurgical patients. The percentage of nitrogen is uniformly high, and since free nitrogen is liberated in the intestine only in small quantities, if at all, it must be derived from air; either directly from swallowed air or indirectly from diffusion from the blood stream, which is saturated with nitrogen. The oxygen figures are low. The percentage of hydrogen and methane are lower in postoperative distention than in medical cases. Since the composition (except for the small amounts of hydrogen and methane) is that of air modified by interchange with the blood gases, the findings are not inconsistent with the view that swallowed air plays a rôle in the production of postoperative distention.

Wangensteen and Rea's¹² experiments with cervical esophagostomy not only proved conclusively that distention was due to swallowed air in obstruction but that distention hastens the death of the animal. He says: "The exclusion of swallowed air obviates the distention factor and, in turn, the sequelae of decreased viability and increased permeability which attend sustained increases of intraluminal pressure—that the mechanical factor of distention and not a 'toxic factor' accounts for the lethal issue in ileal obstruction." We have repeated Wangenstein's esophagostomy experiments and found that no gas could be recovered from the obstructed intestine.

As further evidence that intestinal gases come from swallowed air we have observed that in patients with excision of the esophagus or with complete stricture, with gastrostomy feeding, the absence of gas in the bowel, even in the colon, is quite noticeable.

RELIEF OF DISTENTION

Unfortunately, distention has already occurred in many cases before the patient reaches the surgeon in intestinal obstruction or acute abdominal inflammatory diseases, such as cholecystitis, appendicitis, etc. in which case the problem of removing the gas is paramount. Enemata, purgatives, eserine, pituitrin and other drugs are generally not dependable and are better employed sparingly. The use of gastric or gastroduodenal suction may remove some of the gas from the intestine, but, more important, it will prevent further distention, and the absorption of some gas will occur, giving a degree of relief. After distention has occurred the problem of removing the gas is a difficult one either in dynamic or adynamic ileus, chiefly because the nitrogen is not absorbable.

GASEOUS DISTENTION OF ABDOMEN

McIver, *et al.*,¹³ found that the rates of absorption of intestinal gases varied:

Nitrogen has a very low rate of absorption because the blood and tissues are saturated with N_2 (of an atmospheric pressure). Swallowed air is 79 per cent N_2 , and intestinal gases are 70 per cent N_2 . Thus, we conclude that gaseous distention is largely the result of swallowed air, and we, further, see why distention is not relieved by the absorption of the intestinal gases.

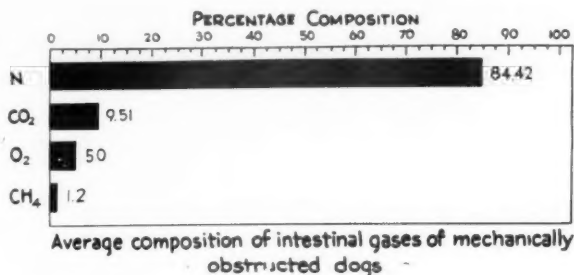


CHART 1.

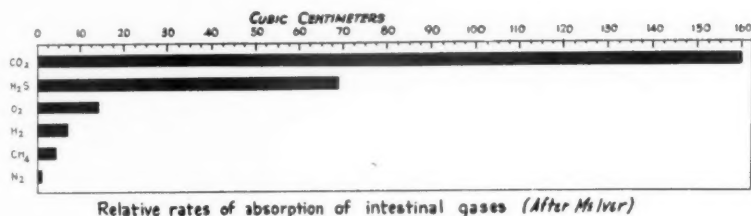


CHART 2.

Furthermore, when the intestine becomes distended, resulting in venous stagnation, CO_2 , instead of being absorbed by the blood stream, as occurs normally, is diffused from the blood stream into the lumen of the bowel, thus increasing the distention.

If no more air is allowed to enter the intestine, gastroduodenal suction, aided by reversed peristalsis, will remove a considerable amount of gas. This was the experience of Wangenstein early in its use. Some gas is absorbed by the blood stream and some observers have succeeded in increasing this absorption (nitrogen) by breathing a *high concentration of oxygen*. Fine and Sears¹⁴ found by inflating a closed loop of bowel with N_2 and another loop with hydrogen, that nitrogen was absorbed from the intestine in small amounts if air was breathed. If pure oxygen was breathed, the absorption was much more rapid. They also observed that these gases were not absorbed from the stomach as rapidly as from the intestine.

Congdon and Burges,¹⁵ as well as Binger, Faulkner and Moore,¹⁷ report experimental and clinical experiences to justify the use of concentrated oxygen in the relief of distention.

Rosenfeld and Fine¹⁷ say: "Breathing of 95 per cent O₂ results not only in a striking decrease in gas volume but also in a marked reduction in the pressure within the lumen of the intestine. The lethal effects of a sustained high-grade gaseous distention are thereby delayed or entirely avoided." They found that clinically, therefore, *pure* oxygen inhalation over periods of 12 to 24 hours reduces intestinal distention. Also, it was found that intermittent breathing of oxygen was almost as efficacious as continuous breathing of it. (Though our experience is confined to only a few cases we have thought its use of some benefit.)

The giving of concentrated oxygen is not without danger; overdose may result in oxygen poisoning with pulmonary congestion, liver congestion and right heart failure (Paine, Keys and Lynn¹⁸).

The Miller-Abbott tube, in cases of intestinal obstruction, is quite useful and often life-saving, but there are frequently technical difficulties in passing the tube which has prevented universal success with its employment.

PREVENTION OF DISTENTION

Gastric Suction and Its Advantages.—We wish in this paper to stress the importance of the *prevention of gaseous distention* rather than the relief of distention after it occurs. The recognition of the frequency of postoperative distention and the realization of the seriousness of distention as a complication, caused us to adopt the practice of using gastric suction routinely in all abdominally operated patients and we have continued this practice for the past five years.* The result has been that postoperative distention is no longer encountered.

The problem of keeping air out of the intestines is a simple one. McIver¹¹ in 1926 used an indwelling tube in the stomach postoperatively to prevent distention, but said: "Since it is occasionally a source of annoyance to the patient, its use indiscriminately is not advocated; but in certain cases in which distention is feared as a grave complication it should be employed."

The plan we have followed is as follows: A Levin tube† is put in place just before the anesthetic is started and allowed to function throughout the operation and until peristalsis has been restored. The tube is kept open by drinking water which the patient enjoys to the extent of tolerating the tube. In 24 to 48 hours the tube is clamped for three hours and the water which is taken by mouth is measured. The tube is then released and the returned fluid measured. If little of the fluid is recovered, it is felt that peristalsis has returned and the tube is removed. On the other hand, if all the fluid is returned suction is continued. In complicated cases such as peritonitis and

*In young children, with operation in the early stage of appendicitis, without peritonitis, we have not routinely used suction. The reflexes being more highly developed in the young, peristalsis is restored more readily and prolonged ileus rarely occurs.

†The tube should not be smaller than a No. 16 F. It is inserted just past the first mark, and must be kept open at all times.

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intestinal, gastro-intestinal and gastric resections, suction is continued for a longer period of time. The average length of time for postoperative suction in common operations is as follows:

- (1) Uncomplicated appendicitis, 24 to 36 hours.
- (2) Ruptured appendix with drainage, 48 to 72 hours.
- (3) Cholecystitis, or cholecystectomy, 48 hours.
- (4) Resection of stomach, 72 to 96 hours.
- (5) Resection of cecum, 72 to 96 hours.
- (6) Resection of rectum, 72 to 96 hours.

We have made a clinical study of some 500 patients who had abdominal operations, upon whom gastric suction was employed, and compared them to a long list of patients with similar operations before gastric suction was practiced. While this study has been tedious and in many ways incomplete, the general conclusions drawn are to the effect that:

- (1) Gastric suction correctly used prevents *postoperative distention*.
- (2) When the abdomen is opened the stomach is empty and collapsed, the advantage of this is evident.
- (3) There is no postoperative vomiting.
- (4) There is no distention, with the discomfort that goes with distention.
- (5) Peristalsis is restored much sooner if the bowel is not distended, and if air is not allowed to pass into the intestine until the bowel recovers, distention does not occur.
- (6) Wound healing is more satisfactory, with few postoperative herniae, and no disruption of wounds.
- (7) There is a lowering of morbidity and of mortality.

Disadvantages.—There are disadvantages to gastroduodenal suction. The most serious criticism of *gastroduodenal* suction is the loss of fluids and electrolytes, in the form of bile, pancreatic juice, and chlorides from the stomach. From a careful study of the problem, we believe that a distinction should be made between *gastroduodenal* and *gastric* suction (Fig. 1). In a series of

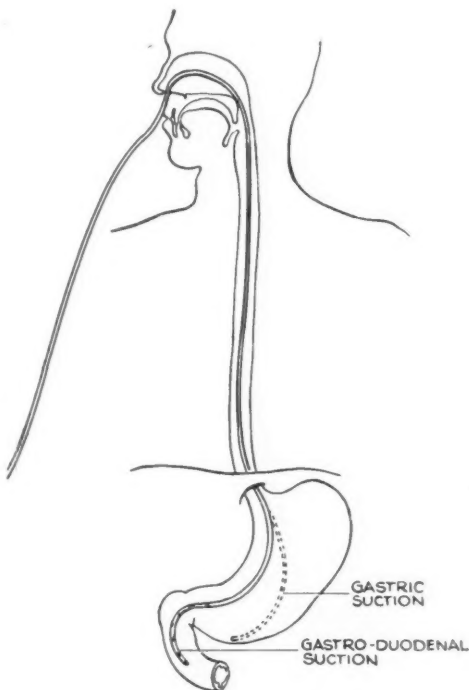


FIG. 1.—Gastric suction as distinguished from gastro-duodenal suction.

observations we found that the *fluid loss* by suction, when the tube extended into the duodenum, was considerably more than when the tube extended only into the stomach. With the tube in the stomach many patients showed little or no bile in the suction fluid. A careful check of a series of more than 75 patients showed that rather than a loss of fluid with gastric suction there was more often a gain during the period of suction with the patient drinking water freely (Table II).

TABLE II
STUDY OF FLUID LOST OR GAINED WITH GASTRIC SUCTION

Patient	Operation	No. of Hours of Suction	Fluid Retained by Mouth	Fluid Lost	Average Amount of Fluid Lost or Retained in 24 Hours	
					Gained	Lost
Mrs. S.	Hysterectomy	58		-595 cc.		-200 cc.
Mrs. W.	Strang. hernia	46	+850 cc.		+425 cc.	
S. B.	Cholecystectomy	48	+550 cc.		+550 cc.	
Mrs. R.	Ruptured peptic ulcer	75	+650 cc.		+200 cc.	
Mr. R.	Subphrenic abscess	46	+1,225 cc.		+650 cc.	
C. T.	Cecostomy	60	+2,000 cc.		+600 cc.	
Mr. H.	Gastro-enterostomy	73	+1,275 cc.		+400 cc.	
Mrs. R.	Hysterectomy	44	+1,140 cc.		+550 cc.	
Mrs. S.	Appendicectomy	28		-950 cc.		-900 cc.
Mr. K.	Cholecystectomy	46	+1,050 cc.		+500 cc.	
Mrs. A.	Colostomy closed	66		-26 cc.		-10 cc.
F. W.	Strang. hernia	25	+1,200 cc.		+1,200 cc.	
N. V.	Appendicectomy	24	+200 cc.		+200 cc.	
P. F.	Abscess. Appendicectomy	30	+150 cc.		+100 cc.	
Mr. W.	Herniotomy	24	+1,200 cc.		+1,200 cc.	
B. R.	Appendicectomy	33	+575 cc.		+450 cc.	
Mrs. H.	Cholecystectomy	49	+2,000 cc.		+1,000 cc.	
A. C.	Ileostomy	52	+75 cc.		+30 cc.	
L. C.	Cholecystectomy	45		-1,195 cc.		-550 cc.
R. M.	Cholecystectomy	47	+2,000 cc.		+1,000 cc.	
Mr. P.	Gastro-enterostomy	84	+2,500 cc.		+600 cc.	
M. D.	Cholecystectomy	42	+1,500 cc.		+700 cc.	
B. C.	Exp. celiotomy	50	+680 cc.		+300 cc.	
Mrs. R.	Obstruction (ca.) —Colostomy	50	+680 cc.		+200 cc.	
E. T.	Hysterectomy	28		-210 cc.		-200 cc.
E. B.	Appendicectomy	24		-800 cc.		-800 cc.
H. H.	Gallbladder drainage	72	+500 cc.		+150 cc.	
Mrs. S.	Appendicectomy— Peritonitis	48	+975 cc.		+475 cc.	
P. L.	Appendicectomy	28	+280 cc.		+270 cc.	
Mrs. S.	Exp. celiotomy	32		-450 cc.		-350 cc.
Mrs. H.	Cholecystectomy	65		-925 cc.		-350 cc.
Mrs. B.	Cholecystectomy	91	+726 cc.		+200 cc.	
G. L.	Appendicectomy	26	+1,200 cc.		+1,200 cc.	
A. E.	Appendicectomy	43	+350 cc.		+175 cc.	
P. K.	Rectal resection	90	+2,100 cc.		+500 cc.	
C. C.	Gastric resection	55	+1,175 cc.		+400 cc.	
Mrs. S.	Cholecystectomy	46	+1,750 cc.		+900 cc.	
Mrs. M.	Cholecystectomy	50	+2,420 cc.		+1,000 cc.	
A. A.	Appendicectomy	18	+50 cc.		+50 cc.	
G. A.	Cholecystectomy	19	+1,000 cc.		+1,000 cc.	
J. V.	Drainage. Appendicectomy	55	+1,500 cc.		+700 cc.	
M. P.	Colostomy closed	24	+1,500 cc.		+700 cc.	
M. B.	Appendicectomy	43	+2,000 cc.		+1,000 cc.	
A. A.	Colostomy Ca. colon	64		-825 cc.		-300 cc.
W. D.	Stab wound	50		-750 cc.		-300 cc.
B. S.	Appendicectomy	37		-150 cc.		-100 cc.
H. C.	Intestinal. resection	60		-515 cc.		-200 cc.
M. H.	Stomach. resection	64		-2,500 cc.		-900 cc.

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SUMMARY

Number of patients.....	50
Number gaining fluid.....	35
Number losing fluid.....	15
Maximum retained per 24 hours.....	1,200 cc.
Minimum retained per 24 hours.....	50 cc.
Average retained per 24 hours.....	562 cc.
Maximum loss per 24 hours.....	900 cc.
Minimum loss per 24 hours.....	10 cc.
Average loss per 24 hours.....	370 cc.

Loss of Chlorides.—On the other hand, an analysis of the fluids recovered with gastric suction showed a definite and regular loss of chlorides as shown in Table III:

TABLE III
AVERAGE SODIUM CHLORIDE LOSS PER 24 HOURS*

Patient	No. of Days Suction	Urine Gm.	Gastric Juice Gm.	Total Gm.
C. M.	4	6.41	7.77	14.18
E. W.	3	5.46	5.11	10.57
C. M.	4	2.28	2.07	4.35
L. P.	1	5.91	2.50	8.41
J. M.	3	4.76	4.59	9.26
W. C.	3	1.32	6.93	8.25
P. H.	3	5.59	4.67	10.26
A. M.	4	3.44	5.17	8.61
Mrs. F.	5	7.88	4.71	12.59
E. M.	2	4.60	1.57	6.17
F. G.	3	5.36	6.73	12.19
Total average		5.1	4.9	9.51

hours—9.81 Gm.

* Patients had no stools nor appreciable amount of sweating during investigation.

This loss corresponds quite accurately with the finding of Coller¹⁹ in his studies of chloride balance. He found that gastric suction removed the equivalent of 3.7 to 4.8 Gm. of salt in 24 hours.

It is unnecessary to say that pre- and postoperative attention to fluid and electrolyte balance in accordance with the principles established by Coller,²⁰ and associates, is indispensable to abdominal surgery and they are of still greater importance when gastric suction is employed. This is particularly true in estimating the amount of sodium chloride to be given.

The annoyance of the tube to the patient is a problem, but the elimination of vomiting, gas pains, enemata, and the discomforts that accompany distention outweigh the discomfort from the tube.

Some reports of damage to the nasal cavity, pharynx, and larynx are found in the literature. We have not encountered any of these. In those cases where prolonged use of the tube is necessary, frequent changing of the tube will obviate this danger.

COMMENT AND SUMMARY

That postoperative distention is a serious complication will be admitted by all. The prevention of distention as a complication of abdominal surgical operations is easily accomplished. The intestinal gases are, for all practical

purposes, composed of swallowed air; and gastric suction, if efficiently employed, will recover this air. Large amounts of air is swallowed during the anesthesia and after the operation. When a patient is nauseated and has a disagreeable taste as is experienced during an anesthesia, and postoperatively, there is, naturally, frequent swallowing in the natural effort to fill the stomach to reflexly stimulate vomiting. Since the patient is in a reclining position, the opening of the esophagus into the stomach is in a dependent position and regurgitation of air does not occur.

Further, we are of the opinion that, if the suction tube does not pass into the duodenum, the loss of fluids (pancreatic juices and bile) will be much less but still the air will be recovered.

The value of this procedure is particularly noticeable in acute *inflammatory intra-abdominal* conditions, as well as in *intestinal obstruction*. Ileus is of little consequence in the absence of gaseous distention, and even in advanced peritonitis cases one can more safely wait for a favorable time for operation by using gastric suction and preventing further distention. It is also true that if the advanced peritonitis patient be operated upon, the prevention of distention following operation guarantees rest of the bowel, maintenance of good intestinal circulation, giving the protective power of the peritoneum much better chance to take care of the infection.

Another very striking occasion where we have found gastric suction indispensable is in the very large abdominal and diaphragmatic hernia in which the intestines have been outside the abdominal cavity for a long time, with a marked reduction in the size of the cavity. These patients were formerly great hazards or impossible operative risks. Forcing the hernial contents back in the abdominal cavity and closing the wound under tension is possible. Keeping the bowel deflated for several days until peristalsis is restored, makes this procedure safe without which a fatality would result.

In operations upon the stomach, intestines, colon or rectum, and more particularly where stomach and intestinal suturing is done, the value of eliminating distention for several days is readily apparent. Enterostomies proximal to anastomoses are no longer necessary. We can say, with all sincerity, that no one thing has contributed so much to the advancement of abdominal surgery in recent times as this simple procedure of keeping the bowel deflated.

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DISCUSSION.—DR. WILLIS D. GATCH (Indianapolis, Ind.): We are indebted to Doctor Singleton for calling to our attention this method of preventing postoperative distention. He is right in his contention that the distending gas is chiefly nitrogen derived from swallowed air. The results he reports convince us of the efficiency of his method. Since I can find no matter for controversy with the essayist. I shall devote my discussion to the amplification of some of the more theoretic points he has made.

Gastric distention is far more deadly than intestinal distention. If the pylorus of a dog is tied and its stomach inflated with a sustained pressure of 25 Mm. it will die of asphyxia in two hours without concentration of the blood. Inflation of its stomach with a

sustained pressure of about 10 Mm. will cause its death in about six hours, and its blood will be considerably concentrated. It may survive a marked inflation of its small intestine for ten to 15 hours.

Patients, as Doctor Singleton has remarked, often swallow great quantities of air in the induction period of anesthesia. The resulting dilatation of the stomach offers a serious impediment to the respiration which, I believe, may be fatal in some cases. We have shown experimentally that distention of the stomach and of the intestine causes marked elevation and fixation of the diaphragm. When this is present the total amount of air which the animal breathes is increased five or six times over normal, but despite this it becomes asphyxiated. When the capacity of the thorax is decreased by elevation of the diaphragm, the lungs are incapable of oxygenating the blood completely and this inability cannot be removed even by the administration of pure oxygen. It, of course, follows that anesthesia is made much safer by deflation of the stomach.

The essayist has discussed briefly the ill effects of bowel distention. The literature on this subject is vast and full of contradictory conclusions. We believe that most of these can be explained and reconciled by the primary conception that the essential effect of bowel distention is to increase the intercellular or tissue pressure in the bowel wall, with results which are made easily comprehensible by Starling's hypothesis on the capillary circulation. The corollary to this conception is that there are two well-defined stages of bowel distention. Thus, if a loop of intestine is inflated with a rather low pressure, it will be found to have a diameter of about one inch. This diameter will remain constant as the pressure is increased up to the point at which rupture of the bowel occurs. If, however, a loop of intestine is tightly inflated and kept in the abdomen its diameter will gradually increase up to perhaps two to three times normal. If the pressure is measured in this distended intestine, it will be found to be comparatively low—probably 10–15 Mm. The circulation in the tightly distended bowel is practically at a standstill. The bowel is pale, bloodless and no fluid collects in its lumen. The dilated bowel is blue, edematous and flaccid. We have shown that its cyanosis is due, not to venous obstruction, but to vasomotor paralysis. Its circulation is present but in a crippled condition. An albuminous exudate collects in its lumen. Its power of absorption is greatly diminished and its walls have been stretched until they have lost the power to contract. The bowel is being injured in the first stage of distention; it is recovering from injury in the second stage. It passes from the first stage to the second stage when its wall stretches enough to lower the pressure to a level at which a continuous flow of blood through its capillaries can occur. Of course, if the intra-intestinal pressure increases as the bowel dilates the second stage will not be found. Very few direct measurements of intra-intestinal pressure in man have been made. Those recorded vary from 111 to 13 Mm. It is interesting to note that Stone and Firor, who report the measurement of 111 Mm., state that the intestine was tightly distended.

When a bowel is found in Stage two of distention, relief of the mechanical cause of the obstruction will not relieve the obstruction for a period of days because the bowel has lost its power to contract.

Our experimental results have led us to believe that the concentration of the blood which occurs when the stomach or intestine is distended is due to asphyxia.

The essayist has referred unfavorably to the use of pitressin in the treatment of post-operative distention. Mann has shown that this drug is dangerous because it causes a great decrease of blood flow in the walls of the heart.

DR. FREDERICK A. COLLIER (Ann Arbor, Mich.): I think we all agree with Doctor Singleton, at least those of us who have done abdominal surgery, that distention can be, and very frequently is, one of the most distressing and not infrequently fatal complications that can occur. I think many in this room can remember back to a time when we felt that this distention was due to fermentation and putrefaction, and the only treatment we had was, as Doctor Gatch has mentioned, cathartics, and enemata of all kinds, variously flavored. I remember one flavor we had was nutmeg. And of course we had the rectal tubes.

As far as I know, enemata do nothing but exhaust the patient, stimulate reverse peristalsis, and increase distention and the rectal tube does nothing but cause piles. I have never seen it do anything else.

While all of us here know now, and have known, of course, that this distention is

due to swallowed air. I can assure you that there are many people in this country who treat distention who do not yet know this, and who hold the older views that I have already hinted. I think it is very timely and very wise that these subjects be discussed and discussed more widely outside of the halls where this Association meets.

I was very much interested in Doctor Singleton's mention of the method of preventing distention by the use of the tube introduced before anesthesia. In our own laboratory, Doctor Moyer has carried on experimental work, and has shown that, particularly in the excitement stage and in the presurgical stage of cyclopropane anesthesia, and to a lesser extent ether, enormous amounts of air may be taken in. For example, a dog weighing from 10 to 15 Kg. may take in, and has taken in under these circumstances, by swallowing, just at this stage and not in the deeper anesthesia, as high as 1,500 cc. of air in three minutes. Associated with this intake, of course, there is always a fall in blood pressure of ten to 35 points, and rapid respiration, and, of course, if carried on it may come to the point where death of the animal will ensue. I had not appreciated how much air can be taken in just at this time, namely, during the early part of the operation. With the tube in the stomach, as Doctor Singleton mentioned, the air is drawn back very quickly and this difficulty is obviated.

Both essayists have mentioned, again briefly, something we all know and something that deserves a great deal of further study, and that is the diminution in the vital capacity in the available air, the residual air associated not only with the operation. We also know that distention further inhibits the action of the diaphragm, and we all, of course, know that this minimizing of the action of the diaphragm renders that patient quite susceptible to atelectasis, which is the commonest of all pulmonary complications. It has been shown many times that anoxia is always associated with the diminution of the vital capacity, and anoxia plus the proneness to atelectasis should, I think, be emphasized again as a very disturbing side light on distention.

There is one phrase that Doctor Singleton used that I think perhaps may be a little misleading, "fluid gained." I think it would be better for Doctor Singleton to say fluid retained. Fluid gained rather implies this is a gain in the total weight of the patient. We know that is not true. The amount that is retained is important. Of course, but it is never enough to supply the fluid needs of the body.

Your measurements, of course, show that 4 Gm. is an average loss of salt per day, which is about a liter of gastric juice. In our clinic—Doctor Maddock presented this to you two years ago—we have found a very satisfactory way of taking care of the salt requirements by replacing it by the so-called volume-for-volume rule. It is lost as hypertonic, and if one replaces that amount with the normal saline, the salt needs of the patient will be cared for without giving an additional dangerous amount.

In conclusion, I would like to urge this society to take the same firm stand against the use of enemata, as we have for long years taken against the use of cathartics in cases of distention.

DR. PHILEMON E. TRUESDALE (Fall River, Mass.): I was very glad to hear Doctor Singleton refer to dilatation of the stomach and its consequences, because I think it is important in case one cannot decompress the stomach by an ordinary small stomach tube. As the stomach increases in size from gases, it continues to enlarge toward the left side and raise the diaphragm. As it increases in dimension, and as the pressure in the stomach increases, there is an angulation at the lower end of the esophagus at the cardiac sphincter, and as the stomach continues to dilate the diaphragm rises, and when the pressure in the stomach has reached a point that is greater than it is in the left pleural cavity, the diaphragm continues to rise until it is in position of eventration. In this position of eventration it displaces the heart and it displaces the entire mediastinum, causing pressure on the right lung, and then, as the pressure increases, the right lung is encroached upon further, and there is an anoxemia.

Now the Miller-Abbott tube under such circumstances is not adequate because it does not drain the stomach, but a small stomach tube of more rigidity than the Miller-Abbott tube will pass through the cardiac sphincter.

I just wish to call your attention to this point, in case of disappointment in using the Miller-Abbott tube at that time, that the use of a more rigid rubber tube, the stomach tube, will pass into the stomach, although the displacement of the thoracic organs has developed to a considerable degree.

DR. WALTER G. MADDOCK (Ann Arbor, Mich.): One of the points I would like to know more about is the mechanics of swallowed air. Doctor Singleton has mentioned one of the possibilities, in the fact of air getting down into the stomach during anesthesia. It has always seemed to me that I have never seen patients with intestinal obstruction, and a lot of distention, doing a great deal of air swallowing.

I have been interested in the problem, and I recall one case vividly, of a child of four who had peritonitis from a ruptured Meckel's diverticulum. We had a plain film of abdomen, and it showed a tremendous pneumoperitoneum, the liver and the spleen clearly outlined, and the intestines outlined in the center of the abdomen. We put a trocar through the abdominal wall and let the gas whistle out, and it did, under considerable pressure. The patient was operated upon about 40 minutes later, being unconscious in the meantime. The pulse was about 160 per minute, respiration 60. By the time that patient got to the operating room the distention—that is, the pneumoperitoneum—was up just as high as it was before we put the trocar into the abdomen.

I am sure there is some mechanism by which that gas gets down into the gastrointestinal tract, and in that case into the peritoneal cavity, that is not actually swallowing. But it is true that is largely atmospheric air.

I have made one experiment in trying to determine how gas gets down. I do know that on respiration the esophagus opens up. The bronchoscopist will tell us the same thing. And the air goes right down the esophagus. In my efforts to see whether it would pass into the stomach in dogs, I failed to find that a definite fact. I thought it occurred in a couple of cases, but the evidence was not conclusive. I think it is an interesting point to keep in mind, that while we are using the term "swallowed air" we still have got a lot to account for in knowing more about the mechanism of the act of swallowing.

DR. ALBERT O. SINGLETON (closing): Doctor Collier is a young man, but he did mention the fact that he remembered when a great many things were done to prevent gastric distention. I know quite well that I spent much more time with the rectal tube, when I was a hospital resident intern, than I did with the stethoscope, in trying to get rid of gas in postoperative patients.

Ileus without distention does not seriously hurt a patient. The bowel may not have peristalsis for a very long time, still if there is little air or gas in it that patient does not become ill.

Doctor Gatch told us many ways in which this distention affect the patients. If one gets a patient before distention occurs, it does not matter what the pathology is, one can prevent the distention from occurring.

We are convinced, after very long and careful study of these patients, that no patient gets distention so long as the gastric suction tube is working. This may be five, six, or seven days. He will be just as flat when you see him five days after operation as he was at the time of operation. The time for gastric suction is before distention occurs. The place for intubation of the intestine is after the distention occurs.

Generally speaking, most patients reach the surgeon before distention becomes marked, even in peritonitis and appendicitis. If they are operable, they are not very badly distended. Following the operation, they should not become distended at all. If you keep the gastric suction working until peristalsis is restored, even though it be a week, the patient will be just as flat and as well off when you get ready to take the suction away. The amount of gas that may accumulate in the intestine in a short time is amazing. Occasionally, we remove the suction too soon, or the suction tube gets stopped-up; within three hours, the patient will be ballooned up, and trying to vomit.

So, by preventing gaseous distention, one goes far to make surgery safe, not only abdominal surgery but thoracic surgery as well. If one keeps the gas out of the alimentary tract for three or four days after the pneumonectomy, the patient aerates himself much better and does not become so ill. So the possibilities of this procedure, simply keeping the air out of the intestine, makes abdominal surgery much safer than it has ever been before.

SMALL INTESTINE OBSTRUCTION: A FIVE-YEAR STUDY*

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DETROIT, MICH.

FROM THE DEPARTMENT OF SURGERY, WAYNE UNIVERSITY COLLEGE OF MEDICINE AND THE DETROIT RECEIVING HOSPITAL

SUFFICIENT time has elapsed since we began a rather extensive use of intestinal suction drainage to permit an analysis of our results over a five-year period. This series includes all cases of small intestinal distention or obstruction treated on the Wayne University Surgical Service at the Detroit Receiving Hospital between January 1, 1937 and January 1, 1942. It is to be emphasized that we have included all cases with sufficient distention to require treatment, whether or not the distention was the primary condition for which they were admitted. There were 332 such cases, this number representing approximately half the total number admitted to the hospital during that period.

For simplicity of classification we have chosen to use that described by Crowley and Johnston (Fig. 1) since it considers the three important factors in all cases of ileus: patency of the lumen, peristaltic power, and circulatory status. Space limitations do not permit detailed consideration, but the results will be briefly listed according to this classification.

OCCLUDED ACTIVE ILEUS—112 CASES

These are cases in which the primary factor is occlusion of the lumen of the intestine, commonly referred to as "mechanical obstruction." One hundred and twelve or about two-thirds of our 332 cases fell in this group. Adhesions were the most common cause, accounting for 94 of the 112 cases of occlusion. (The figure given includes a number of cases of strangulated obstruction more fully described elsewhere.) Twenty-one of these 112 cases of occluded active ileus died, a mortality of 18.7 per cent for this group; this includes all deaths, whether or not directly attributable to the obstruction.

PATENT INACTIVE ILEUS—135 CASES

Loss of intestinal propulsive power is the primary factor in this group; it is the one commonly referred to as "adynamic ileus" or "paralytic ileus." Minor degrees of distention have not been included, this report considering only cases in which the accumulation of gas was sufficient to require active treatment for relief.

Postoperative ileus (47 cases) and that associated with peritonitis (54 cases) comprise more than two-thirds of this group. Twelve cases followed trauma and 22 were the result of various other conditions, among them pneumonia, uremia, liver abscess, and pancreatitis. Twenty-five of the cases in this group died, a mortality of 18.5 per cent for the entire group; this includes all deaths, whether or not directly attributable to the distention.

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ILEUS-TYPE INDETERMINATE OR MIXED—29 CASES

There will always be certain cases in which it is nearly impossible to determine whether luminal occlusion or inactivity of peristalsis is the primary factor. Certain other cases, particularly those with inflammation producing both reflex intestinal inhibition and occlusive adhesions, can only be listed as belonging to both groups. To avoid duplication these are listed in a separate category of "Ileus-type Indeterminate or Mixed"; there were 29 such cases.

Five cases were undiagnosed; presenting marked distention when first seen, they were decompressed by suction drainage and thus relieved of their symptoms. They were not operated upon; roentgen ray localization studies failed to reveal obstruction and they did not redistend subsequent to removal of the tube.

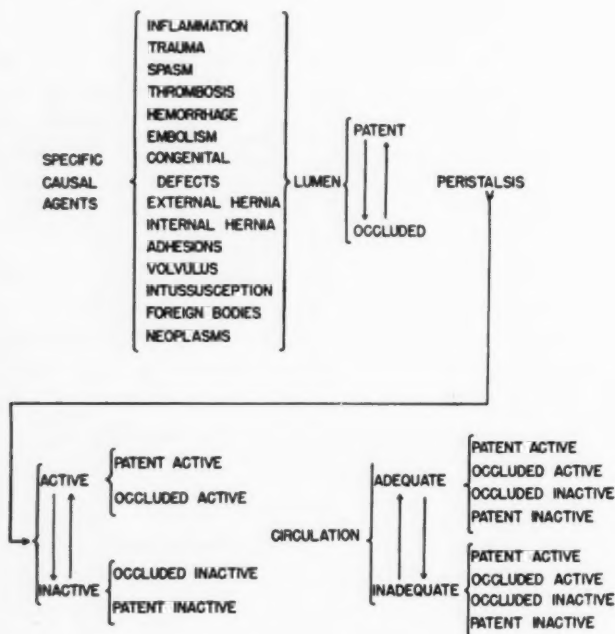


FIG. 1.—Schema for classification of small intestine ileus (Crowley).

Twenty-four cases had both adhesions and inflammation or malignancy and inflammation. This group includes most of the peritonitis cases, hence the high mortality of 12, or 41.7 per cent, of the 29 cases in this group.

INTERFERENCE WITH THE MESENTERIC BLOOD SUPPLY—81 CASES

The mesenteric circulation can be impaired either by strangulation in external herniae or by pressure from some agent within the abdomen; in either circumstance immediate operation is imperative. Because of differences in ease of diagnosis, these two groups are separated for study.

(1) *Internal Strangulation—25 Cases.*—Seven of these were due to

SMALL INTESTINE OBSTRUCTION

adhesive bands, 12 to volvulus, four to internal herniae and one to intussusception. There was one case of mesenteric thrombosis. Operation was deferred in three cases and not carried out in three others; in five of these, diagnosis was in error or delayed, while the sixth was moribund on admission. Internal strangulation was thus correctly diagnosed preoperatively in 19 of the 25 cases. Ten of the 25 died, a mortality of 40 per cent for the group.

(II) *Strangulation in External Herniae—56 Cases.*—Included here are only those cases of strangulated hernia which showed definite color changes of the herniated intestine, with or without petechial hemorrhages in the mesentery. These cases were not included in the study as originally planned, but have been added for the sake of completeness.

Among the 56 cases were 34 inguinal, 13 femoral, five ventral and four umbilical herniae. Four required resection of intestine, and three of these died. In all, eight cases died, a mortality of 14.3 per cent for the hernia group.

METHODS OF TREATMENT

Throughout the period covered by this report, our primary consideration has been the relief of distention, usually by some type of suction drainage (gastric 53 cases, duodenal 39 cases, intestinal 180 cases). Enterostomy was performed but five times, cecostomy twice. In most of these cases the procedure was a futile gesture and had little effect upon the outcome.

In occluded ileus, operation was carried out within the first 24 hours when mesenteric vascular interference was suspected or when the cases were seen early before marked distention had developed; all other cases were subjected to a period of preparatory decompression with concurrent restoration of lost fluid and electrolytes. Nonoccluded cases usually required only decompression, fluid and electrolytes, and treatment of the primary disease condition which caused the distention.

SUMMARY

(1) Three hundred and thirty-two cases treated for small intestine obstruction, with or without distention, have been studied and the results briefly summarized.

(2) Fifteen, or 4.5 per cent of the deaths, were directly attributable to the patients' obstruction. Distention, however, may well have been an important factor in many of the 43 other deaths.

(3) Therefore, we feel that the total number of deaths, from whatever cause (66), is the figure which should be considered. This makes the mortality 19.9 per cent for the entire group.

DISCUSSION.—DR. ALLEN O. WHIPPLE (New York): There are two points that I should like to bring out in connection with the last paper. Our clinic has been a very strong advocate of intestinal intubation, and we now have some 510 cases that have been intubated. I am not going to go into the details of statistics, but I want to bring out two points, or discuss two phases of this subject. One is the so-called paralytic or dynamic ileus. Doctor Lee, of our clinic, has recently published a study of a series of cases in which a paralytic ileus was very definitely associated with a low serum protein and a definite evidence of edema of the bowel. Many of the cases of peritonitis where there has been a marked loss of protein in the exudate in the peritoneum developed this type of peritonitis. Another group.

which was the result of overhydration and overenthusiasm in giving salt solution in the presence of a low serum protein, developed this same type of edema of the bowel wall, causing a loss of function of the bowel.

The other group of cases that I would like to speak of is that of right colonic resection. Intestinal intubation in that group of cases has produced an amazing lowering of mortality in our clinic.

In some 39 where intestinal intubation has been used as a preoperative measure, we have lost only one case. That is based upon a very definite and sound surgical principle, and that is that you remove tension from the suture line. I am not speaking of the right colon section with ileocolostomy. Whether that is an end-to-side or side-to-side anastomosis, I do not think makes much difference, but the keeping empty of the proximal loop, of intestine that is sutured to the colon, makes it possible for the initial sealing-off of the peritoneal suture line, the prevention of tissue necrosis due to distention, and insures a smooth postoperative course.

The combination of intestinal intubation, together with the preparation of the patient beforehand, bringing his metabolism to normal level before operation, and the use of one of the sulfonamide compounds, sulfanilamide, or sulfadiazene, by way of frosting the anastomotic line, I believe will make a tremendous difference in the right-sided colectomies. In left-sided colectomies, the intubation is of relatively little use, and in those cases I am still firmly convinced that a preliminary cecostomy, even in the absence of obstruction, is a very important safety factor, but all of the measures that have been spoken of are really based upon the removal of tissue tension from the suture line and maintaining the blood supply to the intestine.

It seems to me that the intestinal intubation has introduced a new safety factor in abdominal surgery which cannot be overestimated.

DR. R. J. NOER (closing): In regard to Doctor Gatch's statement about the internal strangulations and the delay in operation: perhaps I did not make myself entirely clear on what we meant by immediate operation. Those which were listed in the tables as "immediate operation" were performed within the first 24 hours. Most of them had at least a few hours' delay for restoration of their fluid and chemical balance. Thirty-one cases were operated upon within the first 24 hours, and 25 had later operations.

We are not willing to bring ourselves to the point which Doctor Gatch suggests, that even in the presence of internal strangulation these patients can be allowed to wall-off, as does an appendiceal abscess. However, we did have an interesting patient received from another service rather late in the course of her disease, who had a large mass and evidence of intestinal obstruction for many days. Her abscess was drained and the patient subsequently died of pneumonia. At autopsy, we found that about two feet of intestine had sloughed off and a fairly good anastomosis had been established. She was not treated that way by election, but it is mentioned as an indication that what Doctor Gatch says does occur.

With regard to Doctor Truesdale's statement about the difficulty in passing the Miller-Abbott tube into a dilated stomach, I might say that for several years we have almost never used the standard commercial Miller-Abbott tube, partly because of its greater degree of flexibility. We make up our own balloon-tipped tubes with a No. 16 or No. 18 Jutte tube. This is stiffer and much easier to manipulate, and we believe just as efficient in the stomach or duodenum as the standard stomach or duodenal tubes.

We would certainly agree with Doctor Singleton on the use of the stomach tube in prophylaxis. We find, as I mentioned, with cases of peritonitis, that with a tube in the stomach, a fair number of these patients never become distended, and the intestinal tube is, therefore, not required for treatment.

VITAMIN DEFICIENCY AS A FACTOR IN THE ETIOLOGY OF SURGICAL DISEASES OF THE DIGESTIVE SYSTEM *

FRANK K. BOLAND, M.D.

ATLANTA, GA.

DESPITE the tendency of vitamins to become a fad and with the opportunity they provide for commercial exploitation, definitely known facts about them appear to merit attention. The reality of certain vitamins, and their influence on certain diseases, seems well proven. Inadequacy of vitamins B, C and D as causative factors in beri-beri, scurvy and rickets, respectively, is recognized. On the other hand, it is felt that other pathologic conditions may be due to vitamin deficiency, although it is difficult to prove which vitamin is involved, or it may be that the lack of more than one vitamin is responsible.

Surgery is concerned but very little with the diseases mentioned above, and it is found that most diseases in which avitaminosis plays a part rarely require surgical treatment. However, it is important for the surgeon to consider carefully vitamin deficiencies as part of the preoperative and postoperative care of patients. The direct, immediate causes of the lesions under discussion, ulcer of the stomach and duodenum, gallbladder disease and appendicitis, sometimes are understood and often are not. It is with the remote, underlying, or predisposing causes that we are concerned in this paper. Such causes also might be classed as preventable, which direct causes are not.

Interest was aroused in this subject 35 years ago when the scarcity of these diseases was observed among the Negro patients in the Grady (municipal) Hospital, Atlanta. Appendicitis was rare among Negroes as compared with white patients, while the presence of a stomach ulcer or case of cholecystitis on the Negro wards created a sensation and all the staff wished to see it. The absence of these lesions in the colored population was explained on the ground of "racial peculiarity." The neurogenic origin of ulcer, suggested years later by Cushing, of course, was not thought of.

The remarkable paper of the British surgeon, McCarrison,¹ 21 years ago, gave a different idea. He wrote that during nine years' sojourn in a remote part of India he performed 400 surgical operations annually among the natives, and during this time he did not see a single case of gastric or duodenal ulcer, appendicitis or ulcerative colitis. Gallbladder disease was not mentioned, and ulcerative colitis is removed from the present discussion because the sulfonamides have almost eliminated this lesion as a surgical entity. At the same time, ulcerative colitis has been as uncommon in Negroes as gastric ulcer.

McCarrison decided that the absence of these diseases among the East Indians was due mainly to the character of the food which they ate. Their food came from the area in which they lived—milk, eggs, grains, fruits and vegetables. They indulged in very little meat, and the amount of sugar consumed in a community of 30,000 people in a year was not as much as used in one of our large hotels in one day. McCarrison believed that the fresh, natural foods

* Read before the American Surgical Association, Cleveland, Ohio, April 6-8, 1942.

of the natives abounded in vitamins, and that the presence of vitamins was a factor in the prevention of these diseases. Specific vitamins were not designated; their identity was not so well recognized as today. That it was not necessary to ship the foods any considerable distance, and that they were eaten soon after being harvested, made preserving them by canning and other means unnecessary thus maintaining their maximum vitamin strength.

McCarrison had evidence that racial peculiarity plays but a small part in the etiology of certain diseases. He watched the health of a large group of natives who had been under his care and who were compelled to move to another district where their former foods were not available. Immediately many of these people developed sicknesses which did not affect them while partaking of their accustomed nutriment. McCarrison at this time further proved his contention as to the results of faulty foods in experiments upon wild monkeys made to subsist upon unnatural, artificially prepared diet.

Another proof of the small part played by racial peculiarity in the cause of disease is shown by Garber,² in his study of the Eskimos. His paper also indicates that vitamins are factors in the prophylaxis of the diseases under consideration. He states that "such maladies as appendicitis, stomach and bowel disorders, cancer, dental decay and many other diseases in the category of the white man's bodily ailments are unknown to the Eskimo. But as soon as he abandons his own diet of fish and meat, even in part, and begins to eat the white man's food, all these ailments appear." Upon what flesh does the Eskimo feed that he does not have the stomach ache? It is well to say "flesh" because he subsists entirely upon flesh—and fish; no bread, no fruit, no vegetables. Such food must be rich in vitamins since this is the only opportunity to obtain them. Thomas³ tells us that fish subsist largely upon marine vegetation, and reminds us that all "flesh is grass." Thus meat and fish come from plant life, the chief source of vitamins.

The question is often asked: "Since Reginald Fitz called the attention of the profession to appendicitis only in 1886, how long before that time was the disease supposed to exist?" While our predecessors in medicine of 200 years ago did not possess the facilities for diagnosis which it is our good fortune to have, nevertheless they were intelligent men, and good observers, and if such a disease as appendicitis had been at all prevalent they would have recognized it and would have written about it. No doubt there were some cases, generally called peritonitis, or something similar, but no considerable number of such cases is recorded. The proposition is advanced, therefore, that appendicitis is mainly a disease of the nineteenth and twentieth centuries.

Gastric and duodenal ulcers and cholecystitis may be grouped with appendicitis in the discussion. It is impossible to explain satisfactorily just why these lesions have appeared in such vast numbers only so recently. The rôle played by avitaminosis is suggested as a partial answer to the problem. The exigencies and complexities of modern life have prevented man from eating only the foods raised in the area where he lives. It now seems essential to preserve large quantities of food and transport them great distances when the customs of the modern table require many of them to be overprepared before

they are consumed. Canning is the principal means of preservation, and while this method may not lessen other nutritive values, there is evidence that canning destroys or impairs vitamin content. The canning of food came into existence in 1810, and was invented by the Frenchman, Nicholas Appert, acting under the instigation of Napoleon Bonaparte. Before this time certain foods had been preserved by drying, pickling and smoking, but were not at all in common use. Napoleon, asserting that an army travels on its stomach, desired to give his soldiers foods retaining as nearly as possible their natural condition by keeping fruits, vegetables, meats, broths and milk in a moist or liquid state. Thus began the era of the home and commercial preservation of foods in cans and other air-tight containers, which, while apparently unavoidable and necessary, may have had something to do with bringing about the era of vitamin deficiency and the introduction of new ailments for the human race.

Experimental evidence is wanting as to the relation between vitamin deficiency and gallbladder disease and appendicitis, but Smith and McConkey⁴ and others have presented graphic demonstration of the relation of vitamins and "peptic"* ulcer in guinea-pigs. In a previous paper⁵ these authors had shown the connection between lack of vitamins and tuberculous ulceration of the intestine. Routine necropsies on 1000 guinea-pigs fed on stock diet did not reveal a single peptic ulcer. Of 75 pigs fed on diets lacking vitamin C, 26 per cent developed peptic ulcers which were similar in location and in gross and microscopic appearance to those observed in man. Diets deficient in vitamins A, B and D did not cause peptic ulcers if the supply of vitamin C was adequate. Mechanical injury to the mucosa of the duodenum in guinea-pigs fed on an adequate diet was followed by rapid and complete healing, while similar injury to guinea-pigs fed on a diet deficient in vitamin C resulted in the formation of peptic ulcers. Smith and McConkey concluded that peptic ulcer in the guinea-pig apparently is caused by a partial but prolonged deficiency of vitamin C.

The incidence of surgical diseases of the digestive system has increased among the Negroes of the South since the first observation was made 35 years ago, due it is believed, as will be shown, to a changing diet. The difference in the number of cases in the two races, based on the percentage of population, is still marked enough to bear out the claims of the present discussion. Nine general hospitals supply the metropolitan area of Atlanta, embracing a population of 533,000: 381,000 white, and 152,000 colored. There are seven hospitals for white patients, and two for Negroes. The vast majority of the patients in this district patronize these institutions; many patients come from other parts of the state and country, while a considerable number of patients go to hospitals outside the territory. During the past five years (1937-1941), among white patients admitted there were 1343 cases of ulcer of the stomach and duodenum; 2940 cases of gallbladder disease, and 16,372 cases of all types of appendicitis. During the same period, among colored patients admitted there were 130 cases of ulcer, 98 cases of gallbladder disease, and 974

* Used for brevity; "gastric and duodenal ulcers" is preferred.

cases of appendicitis. These figures, which are approximately correct, show that during the past five years ulcer was eight times as common in white patients as in Negroes; gallbladder disease was 15 times as common, and appendicitis eight times as common. Inquiry reveals the fact that the relative frequency of these diseases in the two races in other Southern cities is about the same as that reported from Atlanta.

The question has been asked whether the Negro patients receive as thorough study as the white patients. The Negro Division of the Grady Hospital is operated by the Medical School of Emory University, so that these patients are assured diagnostic and therapeutic care on par with that of white people. Again, inasmuch as an equal number of white and colored patients, 50,000 of each, were treated in the hospital during the five-year period, 1937-1941, and since the colored population of the Atlanta area is less than one-third that of the whites, it is probable that more than 90 per cent of the Negroes afflicted with the lesions under discussion were treated in the Grady Hospital. A small per cent were unrecorded, or were treated in a private hospital for colored patients.

The food of the Southern Negro compares in a measure with that of McCarrison's East Indians, and probably would be exactly duplicated if possible. The Negro's first choice in diet is fresh green vegetables, turnip greens, collards and cabbage, and a mixed juice made from them, called "pot likker." They enjoy other vegetables like cow peas, string beans and potatoes, and eat various cereals. Their favorite bread is corn bread, made from water-ground meal when it can be obtained. They will eat fresh fish every day if they can get it, but do not consume a great amount of meat, except the cheaper kinds of bacon; and are not especially fond of sugar and sweets. Pork chops are highly esteemed but are not generally included in the menu on account of the expense. The same reason applies to chicken despite the Negro's traditional affection for this fowl. Coffee and tea do not appeal to their appetites, but they relish lemonade, even for breakfast. High cost precludes liberal use of milk and eggs. In contrast with the more expensive, over-prepared food of most of the white inhabitants, according to our knowledge of the subject, the chosen nutriment of the Negro, while cheap, is rich in vitamins.

Close inquiry reveals the fact that most of the colored victims of the diseases under discussion have strayed from the foods listed above, and either from choice or necessity have indulged in the fare of modern civilization. Some of these patients lived in the homes of white people where they could not obtain a sufficient amount of the nutriment which agrees with them so well; or their occupation forced them to dine at lunch-counters where the can-opener is used so freely. Negroes do not eat canned foods, and it is most unusual to find such an article in their homes. As the members of this race take on more and more the dietary of the day, however, alimentary diseases increase among them.

The loss of vitamins by canning varies with the kind and condition of the food used, and the method of canning. Improved methods are in vogue today which seek to preserve vitamins and other nutritional qualities by the elimination of all air from the cans. The analysis of raw, cooked and canned samples

VITAMIN DEFICIENCIES IN SURGERY

from various sources, given by Pett and Cantor,⁶ show the stability of vitamins under canning as follows:

Vitamin A is fairly stable to heat in the absence of air, and loses from 10 to 50 per cent vitamin content from canning, whether in the home or factory.

Vitamin B₁ is appreciably destroyed in all cooking and canning. Acid products preserve it best, the loss of being 5 to 15 per cent; but in alkaline products 80 per cent may be lost.

Vitamin B₂ complex is more stable to heat. Riboflavin and nicotinic acid are destroyed to the extent of 5 to 20 per cent.

Vitamin C is the least stable of all vitamins, but owing to the occurrence of precursors or combined forms it is stable to canning in some foods; in other cases it is completely destroyed.

Vitamin D is fairly stable in milk; it is not important in most other foods.

These authors conclude that since canned foods must be cooked again in the home, further losses in vitamin content will be noted. This fact tends to bring the value of canned foods even lower than foods which require only one cooking. Therefore, canned foods may sometimes be justified mainly on grounds of convenience and price rather than for their food value.

While vitamin deficiency is only suggested as one of the causative factors in the production of these lesions, further experimental work may result in more definite proof. Infection is one of the principal etiologic agents in cholecystitis and appendicitis, and it has been shown in the laboratory that lack of Vitamins A and B complex lowers resistance to infection from 50 to 75 per cent.⁷ Study of the cause and prevention of disease is equally as important as its diagnosis and treatment.

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DISCUSSION.—DR. J. SHELTON HORSLEY (Richmond, Va.): This paper of Doctor Boland's is very interesting and thought-provoking. Those of us who were born and raised—I suppose I should say born and reared—in the South, along with the Negroes, have evidently noted the change in the incidence of diseases, certainly during the last 25 or 30 years. The effect of vitamins on the Negroes and on the Whites is, of course, rather marked. The "pot liquor" that Dr. Boland spoke so eloquently about is probably one great source of vitamins. It has been made nationally famous by some of our Southern senators who use it in "dunking," but whether used that way or not, it does contain, among other vitamins, considerable vitamin K, because, as you know, vitamin K

comes from alfalfa, among other things. It seems to be not too much of an assumption to think it comes from that, too. Vitamin K which, as you know, has almost transformed the surgery of jaundice, is extremely important and is synthetically prepared.

There is a very interesting correlation between the vitamins and the repair of wounds. It is common knowledge that ordinary wounds on patients who have some vitamin deficiency repair much more rapidly when this deficiency is supplied.

In regard to cancer, vitamins are recently becoming very interesting, especially vitamin H, which has recently been offered and now prepared in crystalline form. Two years ago this was found to be one of the stimulating elements of growth, and it was found in rapidly growing cancers. It may, in a way, now explain the cause of rapidly growing sarcomata, in which there is a streptococcic infection. Vitamin H, or biosin, is found very abundantly in rapidly growing malignant tumors. It is also found abundantly in embryos and in young children.

The streptococcus also demands a large amount of biosin, so that when a wound is infected with streptococci it may consume so much of the biosin that the malignant cells cannot live. That seems to be probably the most logical explanation of those cases in which cure has followed streptococcic infection or in those cases in which Coley's fluid has been followed by cure. While only a few, there are undoubtedly some.

About six years ago a Japanese investigator found one of the benzene rings through the neozobenzene, I believe, called butter-yellow. It has no connection with butter. It is just called butter-yellow because it resembles it in color. It is a very remarkable karyogenic preparation. If that is fed to rats that are on a low-vitamin diet of polished rice, carcinoma of the liver develops in about 90 per cent of the rats. Now, if the rats are given a fairly good vitamin diet, the carcinoma incidence drops to about ten. But if, on the other hand, they are given biosin, the carcinogenic substance breaks through this resistance and goes up to 90 again.

There is a preparation of egg-white, called abidon that seems to counteract the effect of biosin to some extent. While that looks like, suggestively, a remedy for cancer, clinically, does not work out.

Sydenstricker, of Augusta, Ga., did some experiments on this, giving large quantities of it, and produced symptoms quite like pellagra avitaminosis. However, there is a possibility that something may arise through this. There are two different substances, one antagonistic to the other. Egg-white, abidon, of course, is in egg-white or albumin, and can be extracted.

DR. FRED B. LUND (Boston, Mass.): I was delighted to hear Doctor Boland call attention again to the importance of vitamins among patients who have surgical diseases. As some of you know, I have studied some of the vitamins, particularly vitamin C.

In our thinking about these vitamins, we have to be quite careful about drawing definite conclusions as to cause and effect. As recently as seven years ago, some very excellent observers stated that lack of vitamin C was a contributory cause of secondary anemia. Two years ago the same observers restudied the problem a little more carefully, and came to the conclusion that they had been wrong the first time and that what had occurred was that the patients who came into the hospital with dietary secondary anemia were suffering from two separate diseases, that the same diet that was deficient in iron was also deficient in vitamin C, but the vitamin C deficiency had nothing to do with the anemia.

Gastroduodenal ulcer in the human has not, so far as I know, been shown to be caused by lack of vitamin C. I have some data, which are as yet unpublished, showing that 90 per cent of the patients with gastroduodenal ulcer, as seen at the Boston City Hospital, have less than saturated levels of vitamin C in the blood, but just a few patients come in with ruptured gastric ulcer, with obstructive gastric ulcer, bleeding gastric ulcer, who have been taking sufficient orange juice or other sources of vitamin C, and have perfectly normal reserves.

The situation in regard to the low vitamin C I think is a matter of choice of food, and the fact that the population as a whole and many of the doctors have not caught on to the fact that if you push the milk and cream up very high in the diet and do not make a special effort to call their attention to the things removed from the diet, the patients themselves will be apt to remove too much of the vitamin C foods.

APPENDICITIS IN INFANTS AND CHILDREN:

A FIFTEEN-YEAR STUDY *

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APPENDICITIS occurring in childhood is the most common lesion of the abdomen requiring surgical intervention. The symptoms of the disease are easily recognized where the patient is seen early and an early diagnosis made by process of elimination. However, gangrene and perforation, which occurs earlier in the course of the disease in infants and children, alter the subjective and objective findings and it is frequently difficult to evaluate the clinical picture. The adult is conscious of the discomfort associated with appendicitis and can describe his symptoms. The condition in the young child, however, may go unrecognized and not be appreciated because the symptoms are thought to be the result of a disease other than that involving the appendix.

This study of 1,653 case histories has served to emphasize certain facts. Chart I indicates that there is a progressive increase in the incidence of appendicitis in children up to ten years of age. The repeated administration of some type of cathartic is the rule rather than the exception in the group under consideration. Delay in seeking proper medical attention for many of these patients frequently after several days of illness has been a factor in the development of a well advanced infection at the time of admission, and has tended to complicate the surgical management. Pain is recorded as the outstanding subjective symptom accompanied by nausea and vomiting, although the latter may not be present. Fever is found in the majority of cases. The history, as given either by the parent or child, reveals that the onset of pain was sudden and more or less general around the umbilicus, localizing later, usually in the right lower quadrant. Frequently, the objective findings relating to posture, namely, flexion of one or both thighs on the abdomen together with localized tenderness, rigidity or distention, served as an aid in making the diagnosis. In the group seen early in the course of the disease, the characteristic subjective and objective symptoms indicated immediate surgical intervention. Early operation is necessary in the case of the infant or young child. Procrastination leads to a serious condition which jeopardizes the child's chance for recovery, in spite of the best surgical management.

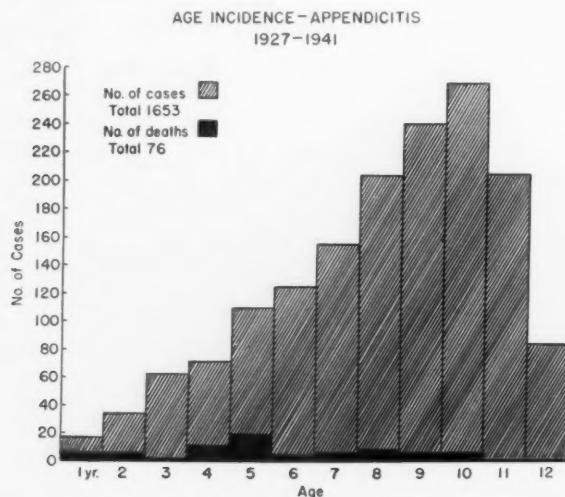
The important problem which confronts the surgeon is the decision regarding the advisability of an immediate operation on the child ill for several days with dissemination of infection throughout a considerable portion of the peritoneal cavity. Individual consideration should be given each patient and certainly no rule can be formulated which sets up an arbitrary type of surgical

* Read before the American Surgical Association, Cleveland, Ohio, April 6-8, 1942.

management. There is, however, general agreement that the patient ill for several days, dehydrated and with abdominal distention, requires a period of conservative treatment to improve the general condition preparatory to surgery.

CLASSIFICATION AND DISCUSSION

This study of appendicitis occurring in infants and children under age 12 includes a review of many patients in the charity class, often undernourished and with low resistance to infection. We believe this fact should be considered in evaluating the results of treatment.



All cases of acute appendicitis have been classified in the following groups: (1) Acute unruptured appendicitis. (2) Local peritonitis. (3) Diffuse peritonitis. (4) Abscess.

(1) *Acute Unruptured Appendicitis*.—The acute unruptured appendicitis group included 742 patients operated upon with three deaths, or a mortality rate of 0.44 per cent. The causes of death were: (1) Pneumonia on the fifth day; (2) intestinal obstruction on the sixth day; and (3) patient died suddenly at the conclusion of the operation; the cause of death was not determined. From the above experience, it is apparent that early diagnosis and immediate operation will give good results. This paper is not particularly concerned with this group of patients, because the morbidity and mortality is minimal.

(2) *Local Peritonitis*.—This group includes the children admitted after an illness of several days' duration with clinical evidence of appendicitis with perforation and local peritonitis. Often considered poor risks at the time of admission, practically all of these patients can be successfully prepared in a few hours by reestablishing hydration. At operation, drainage may be established, and the ruptured gangrenous appendix removed, if this procedure does not unduly increase the time factor or present the possibility of increased contamination of the peritoneal cavity. Chemotherapy and intestinal siphonage are a

valuable adjunct in the management of these cases. There were 183 patients in this group who were operated upon in the 15-year period.

(3) *Diffuse Peritonitis*.—We are particularly concerned with the patients in the third group, which includes children in the underprivileged class admitted to the Surgical Service late in the course of the disease. The picture is often that of a well developed paralytic ileus associated with a high temperature and a rapid, weak pulse. Efforts to prepare these patients for operation have frequently produced little response, and it has been impossible even to attempt simple drainage. Many of these children have rapidly succumbed to the overwhelming toxemia a few hours after admission. Bacteriologic studies from peritoneal aspirations in many of these patients have revealed the presence of mixed infection. With the introduction of chemotherapy, some of these patients have responded satisfactorily and surgery has offered a better prognosis. Duodenal suction or the use of intestinal siphonage has also materially influenced the prognosis and has proved a valuable adjunct in preparing these seriously ill patients for operation. There can be no question but that these methods of intestinal decompression and drainage have contributed in lowering mortality in a group of seriously ill patients. There were 94 patients included in this group.

(4) *Abscess*.—The fourth group of patients, those with localized collections of exudate, are not as serious a problem. The small abscess may or may not be drained at the time, according to the discretion of the surgeon. Short periods of preparation may often be indicated before operation. Our experience has indicated that many small abscesses will rapidly resolve. The large abscesses often are poorly handled by the patient and always present the possibility of rupture and spread of infection of clean areas of the peritoneal cavity. Therefore, in our opinion, relatively early drainage is the procedure of choice. If the appendix is not removed at operation, or in the case of the small abscess allowed to resolve, the parents are instructed to return the child for appendectomy within a period of two months from the time of discharge from the hospital. There were 292 patients diagnosed as having an appendiceal abscess and all were operated upon, although in many instances the surgical procedure was limited to drainage alone. A number of patients not listed here recovered without operation and were discharged to return later for appendectomy. They were then included in the chronic or recurrent group.

PREOPERATIVE MANAGEMENT

The preparation for operation of the child seriously ill as the result of appendicitis with perforation is particularly important. The establishment of physiologic rest of the intestinal tract is indicated as an aid in the prevention of a further spread of infection. This is accomplished by withholding all fluids by mouth, suction drainage, heat to the abdomen and sedation. The patient's fluid balance is reestablished by the administration of saline and glucose solutions, either by multiple infusions or by the continuous drip method. Supplementing intravenous saline and glucose, patients may be given whole blood

or plasma as indicated. When avitaminosis is present in young children with serious peritoneal infection, vitamin therapy is indicated.

SURGICAL TREATMENT

The response to preoperative treatment will decide the time for surgical intervention. The extent of the surgical procedure in the case of the critically ill child with peritonitis must be limited and the decision made as to whether drainage alone is indicated or whether appendectomy can be safely performed. Nitrous oxide and oxygen with a minimum amount of ether has proved a satisfactory anesthetic.

Incisions.—There has been some controversy regarding the type of incision and its relationship to the mortality, especially in the patients with local or diffuse peritonitis. The McBurney incision is preferred by many surgeons. In the case of adults this choice may be justified, but in infants and children it is of less importance, because of the diminished relative distance between the pararectus (Battle) and the McBurney incisions.

During the past five years, 100 patients with acute ruptured appendicitis, with either local or diffuse peritonitis, have been operated upon. In 78 patients, the pararectus incision was used and there were two deaths. In the remaining 22 patients, the McBurney incision was used with three deaths. Good surgical technic and gentle handling of tissues is of greater importance and the mortality is not influenced by the type of incision used in the infant or child.

Drainage.—All accumulations of pus and abscess pockets are opened and evacuated by suction. A soft rubber tissue drain is inserted either into the pelvis or iliac fossa depending on the location of the abscess. Counterdrainage through a small incision in the flank is established as indicated. In closing the wound, the peritoneum is sutured to the point of drainage and a rubber tissue drain inserted beneath the fascia. The remainder of the wound layers are sutured about the drain. In a few instances simple closure of the peritoneum and packing of the remainder of the wound with vaselined gauze have been practiced.

POSTOPERATIVE TREATMENT

Continuation of the methods of preoperative management are indicated until the patient is sufficiently improved to allow removal of suction drainage and discontinuation of the various supportive measures. The immediate continuation of intestinal siphonage following operation has proved of particular benefit as a prophylactic measure as regards paralytic ileus. The application of heat to the abdomen is a routine practice in the patient with distention. Oral fluids are withheld until the temperature and pulse rate approach normal and distention is satisfactorily relieved. Oxygen is also administered to the patient with marked distention. Whole blood or plasma transfusions have proved a valuable postoperative aid in cases of extensive peritonitis.

CHEMOTHERAPY

The sulfonamide group of drugs are gradually assuming more importance in the treatment of patients with peritonitis or abscess formation following

appendiceal perforation. To date the total number of children in this study with intraperitoneal infection following appendiceal perforation who received chemotherapy is not large, but the results have been so encouraging that the continued use of the sulfonamide drugs is strongly indicated. Prior to the year 1939, sulfanilamide was given orally to a few patients. Although no definite conclusions were possible, our opinion at that time was not favorable in regard to this type of therapy. With the introduction of sulfapyridine and subsequently sulfathiazole, the results with patients receiving chemotherapy were encouraging, although not entirely convincing, since the number treated was still small.

The accompanying table lists all patients treated with the sulfonamide drugs during the years 1939, 1940, and 1941, a total of 47 patients for the three-year period. One death occurred in the series, an 18-months-old child under treatment for pulmonary tuberculosis at the time the appendiceal infection developed. This patient succumbed on the twenty-fourth postoperative day from bronchopneumonia. All other patients survived, and in most instances the convalescent period was uneventful. All patients receiving the sulfonamide drugs in the three-year

THE EFFECT OF CHEMOTHERAPY ON THE MORTALITY RATE IN THE PERITONITIS AND ABSCESS GROUP
THREE YEAR PERIOD, 1939-1941.

No of Cases	Chemotherapy	Deaths	Mortality Rate
47	Yes	1	2.1%
67	No	8	11.9%

CHART 2

period had perforation of the appendix with local or diffuse peritonitis or abscess. Twenty-nine patients were included in the abscess group. The one death occurring in the series gave a mortality rate of 2.1 per cent. During the same years, 67 patients in the peritonitis and abscess group did not receive this type of therapy. There were eight deaths or a mortality rate of 11.9 per cent.

It should be pointed out that as experience with chemotherapy indicated a valuable adjunct in the management of the seriously ill patient with peritonitis or abscess, relatively more children received the benefit of this treatment. In most instances they were the seriously ill patients, the type that would ordinarily show a higher mortality. It is, therefore, more convincing evidence that chemotherapy was of benefit since the mortality rate was relatively low.

At present it is our rule to give during the postoperative period sulfathiazole intravenously in the form of the sodium salt to all patients with peritonitis of any considerable extent. In addition, during recent months a majority of these patients have received sulfathiazole powder intraperitoneally at the time of operation. In many instances the drug was also placed in the wound layers during closure. Many patients received intravenous chemotherapy before operation and individuals treated conservatively without operation were given the drug parenterally as early as possible.

As soon as advisable during the postoperative course, oral administration was substituted and continued until the temperature approached normal, and other evidence of peritoneal infection was absent.

We are aware of the argument against the use of sulfathiazole powder intra-

peritoneally or in wounds; namely, the tendency to cake and to act as a foreign body, thus producing added peritoneal and soft tissue reaction. To date, we have seen little evidence that caking of the drug influenced the duration of symptoms or acted in any way detrimental to the patient's chances for recovery. To the contrary, the small group of patients in which the drug was given intraperitoneally or in the wound, without exception, recovered without an excess amount of drainage or delay in wound healing, or a prolonged hospital stay. The amount of sulfathiazole powder placed in the peritoneal cavity has been limited to 2 or 3 Gm. in younger patients and has not exceeded 5 Gm. in older children. Whether small doses of the drug are of benefit may be a question. On the other hand, the small quantities used may account for the absence of irritative symptoms.

Local chemotherapy in the less severe infections or nonperforated cases has not been a part of the management, but probably would prove of benefit as a prophylactic measure against possible contamination of the peritoneum or wound. These drugs have often been employed orally or intravenously in the treatment of complications, particularly pneumonia or upper respiratory infections, with good results as regards ultimate recovery and lowered morbidity.

The amount of sulfathiazole given intravenously or orally is determined according to the weight of the child, a total of 1.25 gr. per pound in a 24-hour period in divided doses at four-hour intervals. The blood levels are usually maintained at 3-5 mg. per cent, although occasional temporary levels as high as 15 mg. per cent have been encountered, usually early in the course of treatment. Unfavorable symptoms attributable to the drug require smaller doses or entire cessation of this type of medication. This has not been necessary in any of our cases to date. Sulfadiazine has been given orally to a few patients, but, since our experience with this drug is so limited, no conclusions can be formulated at this time.

TABLE I
APPENDICITIS—INFANTS AND CHILDREN
1927-1941

Classification	Number	Deaths	Per Cent Mortality
Acute unruptured.....	742	3	0.44
Acute ruptured—local peritonitis.....	183	1	0.55
Acute ruptured—diffuse peritonitis.....	94	61*	64.9
Appendiceal abscess.....	202	11	3.6
Recurrent (chronic) appendicitis.....	342	0	0.0
Total.....	1653	76	4.2

* Includes 35 unoperated.

MORTALITY

There were 183 patients, or 11 per cent of the total number studied, admitted with a diagnosis of ruptured appendicitis and local peritonitis. There was one death in this group, or a mortality rate of 0.55 per cent. Postmortem examination revealed an acute dilatation of the heart and gangrene of the small intestine due to an adhesive band.

In the group classified as acute ruptured appendicitis with diffuse peritonitis

there were 94 patients, or 5.7 per cent of the total group of patients studied. Of this group of patients, 61 died, giving a mortality rate of 64.9 per cent. On further analysis, we find that 35 of the 61 deaths occurred without any operation having been performed. The condition of these patients on admission was critical and attempts to prepare them for surgical intervention were unsuccessful. There were 26 deaths, or a mortality rate of 44.1 per cent, in the remaining 59 patients in this group operated upon. Analysis of the deaths in this group revealed that these patients died of toxemia secondary to overwhelming peritonitis.

In the group classified as appendiceal abscess, there were 292, or 17.6 per cent of the total patients studied. There were 11 deaths, or a mortality rate of 3.6 per cent, with analysis of the 11 deaths occurring in the appendiceal abscess group as follows: one—Convulsions (ether?). Six—Pneumonia. Two Subphrenic abscess. Two—Peritonitis.

The patients with chronic or recurrent appendicitis are listed as a matter of record. There were 342 in this group, with no deaths.

In the groups classified as acute unruptured appendicitis, ruptured with local or diffuse peritonitis, or abscess, there were 1,311 patients, with 76 deaths, or a mortality rate of 5.8 per cent. The mortality for all groups was 4.2 per cent.

SUMMARY

(1) This study represents a review of 1,653 cases of appendicitis in infants and children occurring in a 15-year period (1927–1941) under the care of five members of the Surgical Service, The Children's Hospital of Michigan.

(2) Patients with acute perforated appendicitis with local or diffuse peritonitis require special consideration in regard to preoperative treatment, the optimum time for surgical intervention, the extent of the operative procedure, and the postoperative management.

(3) Chemotherapy in a limited number of patients has proved of definite benefit as an adjunct to the usual routine treatment.

(4) The early diagnosis of acute appendicitis and early operation are the most important factors in lowering the mortality of this disease in infants and children.

DISCUSSION.—DR. WILLIAM E. LADD (Boston): I am sure that most of us agree with nearly all of the statements that Doctor Penberthy has made. We certainly are all agreed that catharsis is contraindicated in appendicitis. We also would be unanimous in the opinion that delay in consulting a physician and a consequent late diagnosis is the chief factor in raising the mortality in this condition. I think most of us who have had much experience with this disease in early life would agree that the younger the patient the more important is the factor of early operation. The problem of acute appendicitis is no problem at all providing it is recognized and an operation is performed prior to the time that peritonitis or other complications have developed. The time limit between the onset of symptoms of appendicitis and the development of complications is apt to be much shorter in early life than it is in the later years.

In a review of 848 cases of acute appendicitis, made three years ago, at the Boston Children's Hospital by one of my associates, there were 466 cases of acute appendicitis with two deaths—one due to hemophilia, which was not recognized until after operation.

This mortality of .42 of 1 per cent is practically identical with the mortality of .44 of 1 per cent just reported by Doctor Penberthy. Other writers report similar negligible mortality in acute appendicitis before complications had developed.

I agree with Doctor Penberthy that delayed operation in these young patients who have developed peritonitis is a hazardous practice. Doctor Ochsner, of Chicago, who was the original advocate of the delayed operation in cases of spreading peritonitis, pointed out over 40 years ago that this practice should not be used in children. Opposition to the delayed operation does not mean that adequate time should not be taken to overcome dehydration and put the patient in the best possible condition for operation. On the contrary, this much delay is very often desirable and of great importance. The indiscriminate policy of delaying operation in cases of spreading peritonitis on the theory that the peritonitis will become a localized abscess is courting disaster in childhood. There is, however, an occasional case in older children in which the peritonitis may become localized and the case changed from the group of bad risks to a group of much lesser risk. To bring about such happy results requires meticulous attention to details of care and the nicest kind of surgical judgment. It should not be attempted in the home by the pediatrician or the general practitioner.

In recent years the McBurney incision has been resurrected, and in my humble opinion rather undue importance has been attached to this incision as a factor in lowering the mortality. If the cecum and appendix ride high up under the liver, a situation not too infrequently found in early life, a McBurney incision is awkward and undesirable. Likewise, if the appendix can be palpated low in the pelvis, the McBurney incision is not suitable. On the other hand, if the appendix is retrocecal and the cecum is in the iliac fossa, the McBurney incision affords an ideal approach. I think the best incision is one made over the appendix so that the offending organ can be removed with a minimum of trauma.

Regarding intestinal drainage by the Miller-Abbott tube, it is our belief that the Miller-Abbott procedure will seldom be required, if the ordinary Wangenstein gastric suction is used as a routine procedure applied at the time of operation and continued as long as indicated.

The addition of chemotherapy to our therapeutic measures appears to be helpful. In a report from our hospital prior to the use of chemotherapy, there were 373 cases of peritonitis of appendiceal origin including the worst cases, with a mortality of 6 per cent. Since the adoption of chemotherapy, we have had 75 cases in which this factor has been introduced. Sulfathiazole has been the drug most frequently used and has been given in sufficient quantities to maintain a blood level of about ten. In these 75 cases, there have been three deaths, a mortality of 4 per cent. One death took place on the fourth postoperative day, and one on the eighth postoperative day, with pneumonia as the determining factor as the cause of death. The third death took place on the eighth postoperative day, with intestinal obstruction and sepsis as the important factors.

In any given series, the main factor in mortality will always be somewhat dependent on the extent of the sepsis at the time of operation. This factor is bound to vary in different localities and in different hospitals in the same locality.

DR. FREDERICK A. COLLIER (Ann Arbor, Mich.): I have no business discussing this paper at all, because my experience in the care of acute appendicitis in youngsters is so much smaller than that of Doctor Penberthy and Doctor Ladd that it is quite inconsequential. Doctor Penberthy asked me to discuss the paper, however, and I think he did so because he regards me as one of the etiologic factors in perhaps raising his mortality there.

In 1930, we reviewed our cases in the University Hospital (adult and children) very carefully, and we found that in both adults and children the death rate occurred essentially in one group: that is, the patients who came in, having had the disease, all with a cathartic, from three to five days. They presented the typical picture so familiar to all of us, of generalized spreading peritonitis. Before that time, we had followed the principle of removing the appendix so that the source of infection could be stopped. We concluded after this study that anything we did would probably give us better results than we had been getting, because our mortality was between 50 and 60 per cent. So we determined at that time to pursue the policy of delayed operation.

Here again, our differences between the policy we have been carrying out and the one mentioned by Doctor Ladd are not factual but only in the phrase I think, because

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after all Doctor Ladd hydrates these dehydrated youngsters, restores their chemistry, puts in a tube, decompresses them, and that is the essence of the delayed operation as we have carried it out. Our mortality in adults and in children is less than it was before.

Doctor Ladd puts his finger exactly on the difficulty, because one talks about delayed operation, and the wrong person delays the operation. It is not the delayed operation. The thing that does harm is the delay between the time of disease and the time the surgeon sees the case. I entirely agree that every one of these patients should be in the hospital under a surgeon's care, and one may delay for an hour, one may delay for ten hours, one may delay for a week. It requires, in my opinion, surgical judgment that I do not have, and that very few do have, to know exactly what is the safe time. As a matter of fact, as we see these youngsters with widespread peritonitis, sick from three to five days, the process in many cases has become irreversible. Nothing one does will effect a cure. That is the point that Doctor Penberthy and I have argued pro and con, and I have rather talked him around. I think, to some delay, and perhaps he feels I urged him too strongly. That is the reason that I discuss this paper to-day.

I would like to mention, however, briefly, the group that we have had our greatest experience with, and that is the college student. We have a large number. I do not know what our enrollment is, but it is fairly large, and we take care of acute appendicitis. These youngsters are supposed to have had some education, and are supposed to be getting more. They probably know as much about acute appendicitis as any group of lay people in the world. Their medical and surgical care, and their hospitalization, costs them nothing, as that is all taken care of by their health service. So the economic point does not enter in. They are, of course, the ideal group. There is no reason why treatment should not be perfect.

Since 1920 to the present time—I do not know the exact figures—we have operated upon them, and in various stages. Some will wait two or three days before we see them. We have operated upon them in all stages of acute appendicitis, local infection, etc., nearly 2,700. That is a rough figure. Three have died in that time. One of them died of infection and gangrene of the bladder. A second died of peritonitis. He remained home in his room and took castor oil for two or three days before we saw him. The third death occurred two weeks after the young man had left the hospital. He was cranking an automobile and died suddenly. I suspected it was an embolus, but we never had any proof because autopsy was not permitted.

Those results show what one can do, and it seems to me they show that diagnosis in an intelligent adult is not too difficult, because we have made many errors but they have been compensated for by the youth and the care we have given this group.

In conclusion, I would suggest to Doctor Penberthy, that perhaps the only way you and I can lower the mortality in these youngsters with peritonitis who live in our neighborhood is to urge upon the mothers that they give the youngsters less castor oil and, as Doctor Boland suggests, probably more "pot liquor."

DR. DAVID E. ROBERTSON (Toronto, Canada): I want to ask your indulgence for a few moments while I show you a few lantern slides.

(Slide) These are the records of cases coming from the Hospital for Sick Children of Toronto, January 1, 1940 to March 27, 1942; total number of appendicectomies, 1,043.

Of these, 465 were definitely acute appendicitis. No mortality in this group. Gross perforation of appendix, 115. Bacteria in free peritoneal fluid, 67. Conservative treatment in 19. Simple drainage in 14. Sulfonamide therapy, 126. Miller-Abbott Tube, 30. Deaths, two.

I thought we had only had one death at the time, but the pathologists very kindly found me a death on the medical side. This patient had been admitted to the surgical ward and had been diagnosed as, apparently, peritonitis, because he was said to have pneumonia on the same side. The Miller-Abbott tube was introduced, and during the first five days it worked rather unsatisfactorily, but they did recover about 1,500 cc. After that, I find by the record, the boy was transferred to the medical side for the treatment of pneumonia, and in another four or five days he died. He was autopsied and was found to have had a ruptured appendix.

(Slide) This was the sixth day of illness, ruptured appendix, with general peritonitis.

Left-side bronchopneumonia. Sulfonamide therapy throughout. I might say that we use the drug intravenously. On the sixth day he obviously had distinct distention.

It is an extraordinary thing that it is so difficult to follow these cases carefully. This lad had a tube introduced that could have been put in just a little farther, and then it would probably have passed on more quickly and gone to the proper route.

(Slide) This shows the seventh day in the morning and the seventh day in the afternoon. The tube is engaged in the duodenum, but it was not allowed to pass on. It was pushed in so that it stayed in the stomach.

(Slide) At the eighth day of illness, it is still in the stomach, and at the ninth day, it is still in the stomach. He was taken over to the medical side, and they reviewed it; the boy died.

I think it is obvious in this boy that, whether or not the distention was the cause of his death, he did have distention, and he had the tube in for all that time, in his duodenum. So if the distention were the cause of his death, a tube in the duodenum is not enough, and the distention down below, whatever the peristalsis there is, will push the gas down to the lowest point, down to the point of obstruction, and that distention of the wall there is what causes the reflex nervous shock, and what I believe to be the cause of death in appendicitis.

The next case is a boy who came into the hospital last October, a year later than this one. He came in with an odd history of having been seen by a physician. The physician called up and gave the history. The physician had seen him the night before, and the boy had a strangulated hernia which he reduced. The child was still ill during the night, and the next morning the physician was called again; the boy again had a strangulated hernia on the same side which he had reduced. The boy was sent to the hospital. He obviously had a general peritonitis. His condition was not fit to warrant an operation for a few hours, until he was put in better condition. He was then operated upon, and found to have a ruptured appendix.

Thinking this boy might have a ruptured intestine from manipulation of the hernia, he had a rectus incision. He did well for a few days, and the next I heard, the resident told me the boy had died. Well, I demanded an inquiry. When a case of appendicitis in a child dies, I believe it is some person's fault. This boy should not have died.

Looking back at his record, I find this picture. (Slide) This boy has marked distention. A tube is put in, crammed in. The tube was left in 18 hours, and nothing came out of it. Three hours before death, they got 250 cc. of fluid out through the tube.

Those are the two deaths we have had. I think they were just due to neglect and misunderstanding of the problems involved. Both of these boys had sulfonamide therapy. I have not believed for a very long time that death in appendicitis is due to bacterial infection or intoxication. I think it is a death that generally occurs about the eighth or ninth day is due to distention. Looking back over the days when we operated freely on these cases, I recall that distention was the factor they all had, the common factor they had before they died. So I believe that death is due to distention, but it is very difficult to make a resident appreciate that.

I have established the custom of seeing every case of this type every day. The resident said a few days ago: "Such-and-such a child is all right, but he vomited yesterday." I said, "Why did he vomit?" "Oh, he just vomited. He's all right." I examined him, and he did not have any obvious clinical distention, but the next picture is this one. (Slide) This was the boy who vomited once five days after operation. The introduction of a Miller-Abbott tube decompressed him, and the boy is well. I think we should critically examine our patients postoperatively.

In our deaths from appendicitis, we should not let any of them be buried or take the pathologist's report as to the condition of the organs, but we should get a true understanding of the distention after the patient's death.

DR. ROBERT ELMAN (St. Louis, Mo.): I just want to add two points from the basis of my experience at St. Louis Children's Hospital. There are two nonoperative procedures which I think are very important, only one of which has been mentioned by Doctor Penberthy; that is, the use of plasma transfusions in amounts which are really large, amounting to about 10 to 20 cc. per kilo.

Dehydration very often is difficult to correct where there is great loss of plasma into the wall of the bowel and general peritonitis, not to mention the peritoneal cavity itself.

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The second point, is the use of oxygen inhalation immediately after the operation, whether the patient is cyanotic or not. In that way, in the very seriously ill patients, anoxia is controlled even before it develops. In many of these very sick patients the oxygen was given to the patient on his way back from the operating room to his room, and he was kept in the oxygen tent for several days.

The use of chemotherapy as well as gastric suction, in our experience, has also resulted in a very marked reduction in mortality. It has also shortened the period of delay, which I think is justified in these very seriously ill patients.

Another factor, the intraperitoneal introduction of sulfanilamide has permitted us to close a great many of these cases of general peritonitis which we would not have cared to do in previous years.

DR. GROVER C. PENBERTHY (closing): I am sure we are all agreed on the early diagnosis and the early operation being essential. I am sorry Doctor Coller misunderstood me. I question very much that he could contribute to my mortality. He was just being facetious. He has done pioneer work, and I am sure we are all agreed with him on the delayed operation.

I think Doctor Robertson and Doctor Ladd are to be congratulated on their mortality rates.

Relative to oxygen therapy, I had to omit some of my paper, Doctor Elman. I am glad you brought that point up, because in addition to the good surgery and the plasma, oxygen therapy is a great help, especially in the child who is tremendously distended.



PUBLISHING AND THE WAR

Perhaps the most striking feature of the present-day European medical periodicals, including the English publications, is that their articles are at least 50 per cent shorter than in the pre-war years. Either the editors must want to save paper, or the authors cannot summon up sufficient mental concentration to write articles of average length. Style has changed also; words are more carefully selected and their subject-matter, mostly related to one or another phase of war medicine, or to public health, is discussed rather more clearly than in former years. Illustrations are seen only occasionally, owing to increased difficulties of printing and engraving, as well as to the high cost of publishing. As far back as the early part of 1941, most of the English medical journals contained announcements by their editors that the illustrations would have to be paid for by the author himself.

One wonders how many medical journals which have long been familiar to us still survive in the so-called Axis countries. We hear almost nothing from Belgium and Holland, and very little from occupied and unoccupied France. In the late November issues of the *Schweizerische medizinische Wochenschrift* are to be found a few abstracts from the French *Presse Médicale*, the *Deutsche medizinische Wochenschrift* and the *Münchener medizinische Wochenschrift*, so we know that they are still in existence, notwithstanding severe military censorship. No doubt many of our favorites have ceased publication entirely. Many editorial offices doubtless have been forced to migrate from one city to another.

—Bulletin of the Medical Library Association, April, 1942.

CLOSURE OF ILEOSTOMY IN ULCERATIVE COLITIS*

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THE SURGICAL TREATMENT of ulcerative colitis has been a recent development with sporadic cases operated upon previous to 1930. During the last decade there has been much interest and progress. The problem confronting surgeons at the beginning of this period was first, to determine what patients could be benefited or saved by surgery, and second, to convince internists under whose care these patients naturally fall, that surgery should not be used solely as a last resort. Through the work of McKittrick, Cave, Stone, Ladd, T. E. Jones, Lahey, the author and others, it has now been accepted that good results follow the employment of ileostomy, partial colectomy, and total colectomy, and that other operations are ineffective and should be discontinued. The medical treatment of ulcerative colitis has been shown to be unsatisfactory in approximately one-half of all cases. Kiefer,¹ in a report from the Lahey Clinic, found that patients who had been under medical treatment and followed for five years or more gave unsatisfactory results in 43 per cent. Ileostomy has been necessary in many of these cases. In spite of improvement in the surgical treatment, there has been no general acceptance of definite indications for ileostomy or uniformity in the time that ileostomy has been elected.

This paper will present our indications for ileostomy and recommend early ileostomy in patients with severe ulcerative colitis in order to obtain the earliest possible remission before irreversible structural changes in the colon occur. Early ileostomy is urged so that the ileostomy may be disconnected, restoring the continuity of the intestinal tract in some patients. There has been a long period of trial for medical management. There has been sufficient experience with ileostomy in late cases to know what results can be expected and in these cases ileostomy must be permanent. Early ileostomy and later closure of the ileostomy has not been given a trial in adult cases. At the Children's Hospital in Boston, Ladd and Gross² have closed the ileostomy of seven children. Stone⁵ reported the closure of five cases in 1929.

Both internists and surgeons have hesitated to advise ileostomy since so doing, in the past, has accepted a permanent fistula of the small intestine. Those not familiar with the management of ileostomy in these cases frequently consider it an intolerable situation, and one that is inconsistent with productive activity. That this is not the case has now been established.³ Nevertheless, if an ileostomy could subsequently be disconnected with safety and without serious recurrence of the disease, this would constitute an important forward step. It should be emphasized, however, that an attempt to restore intestinal continuity by anastomosis of the proximal ileum to a portion of the

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large intestine involved with ulcerative colitis, either in the infective or healed state, should be condemned. In one of Doctor Lahey's early cases in whom a satisfactory remission was obtained but rectal stricture resulted, ileostomy was taken down elsewhere, anastomosing the ileum to the sigmoid colon, against his advice. An operative death followed because of peritonitis. Even though obstruction is not present, the anastomosis utilizing involved colon is almost certain to leak.

We have previously stated in a number of communications⁴ that once an ileostomy is accepted it must always be maintained. There are additional reasons why we previously considered an ileostomy as permanent. In our earlier cases it was performed only in the complicated, advanced cases, usually with marked cicatricial changes in the colon. Furthermore, as soon as the ileostomy is made an even further contraction of the colon occurs from disuse. With clinical remission and healing of the colon as the result of ileostomy, contraction is inevitable. For this reason we do not believe there can be any appreciable change in the policy regarding ileostomy for advanced cases. As previously stated, there has been no clinical trial of disconnecting ileostomies in adults. For this reason we decided to take favorable cases in which ileostomy was definitely indicated, and if satisfactory response was obtained, disengage the ileostomy. After demonstrating this in favorable cases (Cases 1-5), less favorable and unfavorable cases were then tried (Cases 6-9), but no anastomoses of the involved colon have been performed.

INDICATIONS FOR ILEOSTOMY

In order to be able to review critically cases in which ileostomies have been taken down, it is necessary to outline our indications for ileostomy in ulcerative colitis, since obviously if ileostomy were selected for mild cases, closure could be employed with fair frequency. In these, however, medical treatment is usually satisfactory. The indications for ileostomy in our clinic are as follows: (1) Acute fulminating cases, either in a first attack or with recurrent acute attacks; (2) medical failures, including those patients who are incapacitated; (3) massive hemorrhage; (4) subacute perforations, abscesses, peritonitis or fistulas; (5) obstruction; and (6) polyposis including those cases with possible malignancy.

SELECTION OF CASES FOR CLOSURE

We have used three means in selecting cases for closure of ileostomy: (1) We have felt that a clinical remission of symptoms should be maintained for an appreciable period. (2) The inflammatory process must be shown to have healed and be inactive, as observed by sigmoidoscopic examinations. The mucosal surface may still be granular or scarred and may even bleed somewhat on manipulation with a swab, yet any evidence of active infection eliminates the case from closure. (3) The colon must be shown to be distensible by means of a barium enema or double contrast air enema. (Figs. 1 and 2.) Some haustral markings should still be demonstrable, at least in

FIG. 1.

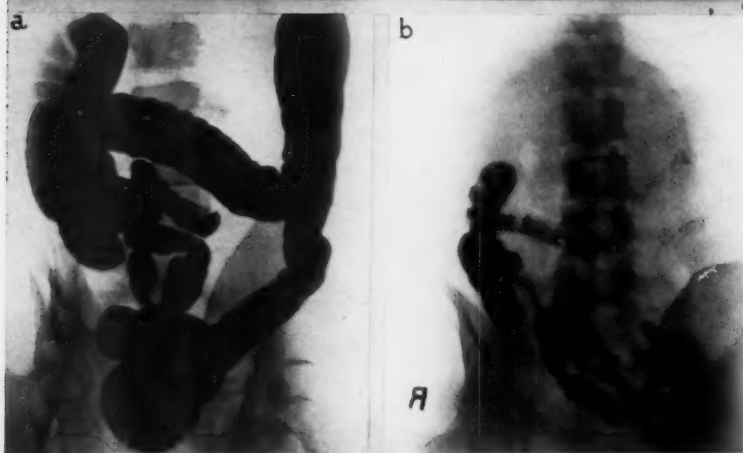
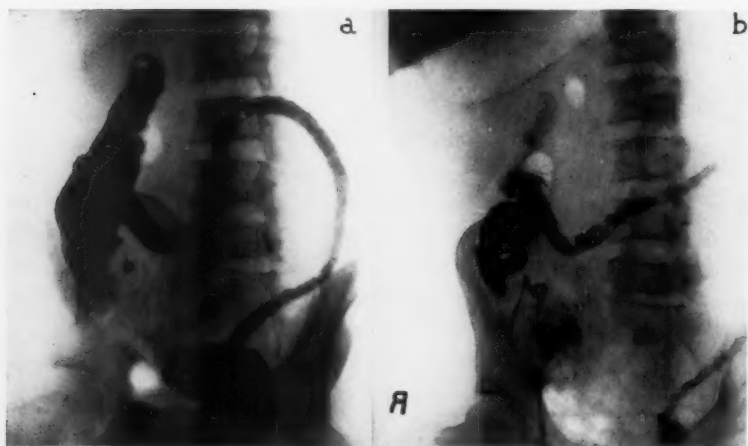


FIG. 2.

FIG. 1.—Case 2: *a*. The full barium enema taken November 10, 1938, six weeks after ileostomy. The sigmoid, rectosigmoid, and right colon distend readily. The remainder of the colon is narrowed but with suggestion of haustral markings. This is chiefly the contracture of disuse as a result of ileostomy.

b. The empty film shows excessive emptying and spasm, with some irregularity of the mucosa. The sigmoidoscopic examination was negative at this time. This is a favorable situation for closure of ileostomy.

FIG. 2.—Case 2: *a*. and *b*. The full and empty barium enema, taken February 23, 1939, three months after closure of ileostomy. Full distensibility and flexibility are demonstrated. The ileocecal valve is incompetent.

the film taken after evacuation of the enema. Haustral markings may be absent in the full enema. An adequate lumen and absence of any local areas of obstruction must be demonstrated. The mucosal pattern should not show pseudopolypoid or too irregular an outline. The following case report will well illustrate the type of serious case of ulcerative colitis in which closure has been carried out (Case 4).

Case Report.—This patient, a man, age 25, first came to the clinic on February 19, 1934, to be examined for possible heart trouble. He was found to have a small, right,

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indirect inguinal hernia. No heart disease was found. In August, 1934, he reported that he was getting along well except that the hernia was larger. He returned to the clinic in July, 1937, because of difficulty in swallowing. At this time, a complete gastroenterologic study was carried out, and a diagnosis made of cardiospasm and nervous exhaustion. Complete examination of the blood, the Hinton test, gastric analysis, fluoroscopy of the stomach, gallbladder test and barium enema were all negative. There was no evidence of ulcerative colitis on roentgen examination after a barium enema.

In January, 1940, the patient had severe low abdominal pain, rectal bleeding and fever. Three weeks before his admission to the hospital hemorrhoidectomy was performed, following which he had severe intestinal cramps and passed many liquid, bloody stools daily. He had been on a strictly limited diet, chiefly of carbohydrates, for seven months. The diagnosis was ulcerative colitis, thrush, and avitaminosis. Agglutination tests for undulant fever and dysentery were negative. The Widal reaction for typhoid and paratyphoid disease was negative. Stool cultures on repeated occasions showed a large amount of yeast, *B. coli*, *Staphylococcus aureus*, and streptococci. An ischiorectal abscess was present, and this was drained the following day. The culture from the pus showed *Staphylococcus aureus* and *B. coli*. He continued to pass a large amount of pus and blood by rectum. Multiple skin furuncles and ulcers of his mouth developed. The high fever persisted; three blood cultures were negative. He was considered too ill to examine by means of a barium enema. Proctoscopy showed the typical findings of acute ulcerative colitis. Treatment with sulfathiazole did not alter his fever or symptoms.

Ileostomy was performed February 7, 1940, without abdominal exploration. An immediate decompression of the ileum was effected. The patient received a blood transfusion on that day, on March 11, and on March 16. Pain developed in the right lower quadrant, followed by the production of an abscess, and later a pelvic abscess developed, which ruptured spontaneously into the bowel. On May 29, a roentgenogram of his colon showed little change in the bowel except in the rectal region. After another blood transfusion he was discharged from the hospital in greatly improved condition on July 19, four and one-half months after admission.

The patient was reexamined on October 19, 1940, at which time there was a sinus around the ileostomy. On proctoscopic examination there seemed to be adequate sphincter control; the mucosa was entirely normal. There was no discharging pus. A barium enema showed good flexibility. The mucosal pattern was found to be within normal limits throughout (Fig. 3).

On October 31, the ileostomy was resected, draining a small chronic abscess of the abdominal wall, and a side-to-side anastomosis of the terminal ileum was performed. Sulfanilamide powder was placed in the wound and the peritoneal cavity. The colon appeared to be within normal limits. There were congenital polyps of the distal small intestine.

On December 20, 1940, after a barium and air enema, roentgenologic examination was negative (Fig. 4). On November 10, 1941, more than a year after operation, the patient weighed 176½ pounds, was well, and had no bleeding. Rectal and proctoscopic examinations gave negative results. He had one formed stool a day. The abdominal wound was firmly healed.

In January, 1942, while working in an airplane factory, the patient was badly burned about the face, hands, and shoulders in an explosion, but he made a good recovery.

March 25, 1942, he had recovered without recurrence of the ulcerative colitis.

CLINICAL DATA

We have closed the ileostomy in nine patients. The first patient was a boy 11 years of age whose ileostomy was closed in 1935 (Case 1). He had a mild recurrence the third week after closure but has been quite well since, for a period of over six years. Our second case was a man, age 38 (Case 2),

FIG. 3.



FIG. 4.

FIG. 3.—Case 4: *a* and *b*. The full and empty barium enema, taken October 15, 1940, eight months after ileostomy. The findings suggest complete healing, with the contracture of disuse due to ileostomy. The proctoscopic examination was negative at this time.

FIG. 4.—Case 4: *a* and *b*. The full and empty barium enema taken December 20, 1940, approximately two months after closure of ileostomy. Except for a more rapid emptying time and spasm, the findings approach those of a normal colon.

with a very acute, fulminating form of ulcerative colitis as a first attack. His ileostomy was closed in November, 1938. He was well for two years and three months, and then had a moderate recurrence at the time of an acute upper respiratory infection. Since that period when he had medical treatment he has been well. During 1939, 1940, and 1941, seven additional cases have been closed. During this period of three years, 50 ileostomies were performed, with five deaths, an operative mortality of 10 per cent. In the group of 45 patients who survived the operation of ileostomy, seven have been closed, or 15.5 per cent of those surviving operation and 14 per cent of all ileostomies during this period. Twelve patients still have their ileostomy

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and are being carried along under medical observation. Some of these are being followed with the expectation that their ileostomies may be closed.

In our group of nine patients, there was one child of 11, who was the youngest of the group; the oldest was 56. The ages of the remainder were 19, 20, 21, 26, 31, 38, and 44. The ages of these patients agree with the general age-group of patients suffering with ulcerative colitis, those of a young adult group. Seven patients were men and two were women. I think without question that the large group of males is partly due to insistence on their part that the closure be done so that they could return to work without ileostomy, since the sex distribution of our cases of ulcerative colitis is about even.

TABLE I

Case	Age and Sex	Duration of Colitis	Duration of Medical Treatment	Indication	Date of Ileostomy	Condition of Colon	Date of Closure	Ileostomy Present	Result
1	11 M.	5 mos.	1 mo.	Med. failure	11/7/34	Favorable	8/13/35	9 mos.	Well (mild recurrence 3 wks. after closure)
2	38 M.	5 mos.	7 days	Med. failure	8/23/38	Favorable	11/22/38	3 mos.	Well (mild recurrence February, 1941)
3	21 F.	2 mos.	5 days	Hemorrhage	1/26/39	Favorable	6/21/39	5 mos.	Very well
4	31 M.	3 wks.	7 days	Acute fulminating, abscesses, fistula	2/7/40	Favorable	10/31/40	8 mos.	Well
5	56 M.	5 wks.	18 days	Med. failure	5/17/40	Favorable	11/26/40	6 mos.	Well (recurrence, October, 1941)
6	44 M.	4 mos.	36 days	Abscess, fistula	12/2/40	Unfavorable	5/16/41	5 mos.	Improved but several stools daily
7	20 F.	3 yrs.	21 mos.	Med. failure	1/10/39	Unfavorable	5/26/41	28 mos.	Failure from obstruction, malnutrition; new ileostomy 3/24/42
8	19 M.	3 mos.	1 mo.	Generalized peritonitis	4/9/40	Unfavorable	10/28/41	18 mos.	Improved but many stools daily
9	26 M.	6 yrs.	3 mos.	Reg. ileitis, recurrent acute	9/11/40	Unfavorable	11/8/41	14 mos.	Failure from colitis; new ileostomy 2/9/42

Only one of our nine patients had had ulcerative colitis for under one month. This was an acute case that had had ulcerative colitis for three weeks and been under treatment for seven days. Many patients with the acute, fulminating form die from their disease even though ileostomy is accepted early. Six of the patients had had their disease one to six months. They represent a group of serious cases and yet have not had their disease so long that the colon had been unalterably changed. One patient had had ulcerative colitis for three years and was a definite failure after closure, as was the patient who had had ulcerative colitis for six years.

A consideration of the indications for ileostomy in this group of nine patients is of interest. Referring to our group of indications for ileostomy we find that ileostomy was elected for the following reasons: (1) Acute, fulminating, one; (2) medical failure, four; (3) hemorrhage, one; (4) infection, two; (5) obstruction, one; and (6) polyposis or malignancy, none.

In addition to determining the duration of the ulcerative colitis, it is important in this group of cases to know the duration of the medical treatment, which was as follows: One to seven days, three; one to four weeks, three; one to three months, two; 21 months, one. The latter case was a failure.

As we first considered the possibility of closure of ileostomy, we felt that a long period of time should elapse before considering closure. These patients had their ileostomy from three to 28 months, the latter one being a failure. Four patients had ileostomy for six months or less; two patients had ileostomy for six to 12 months, while one each had their ileostomy for 14 months, 18 months and 28 months. The patients having ileostomy for 14 months and 28 months were failures, while the one having it for 18 months was unimproved after closure.

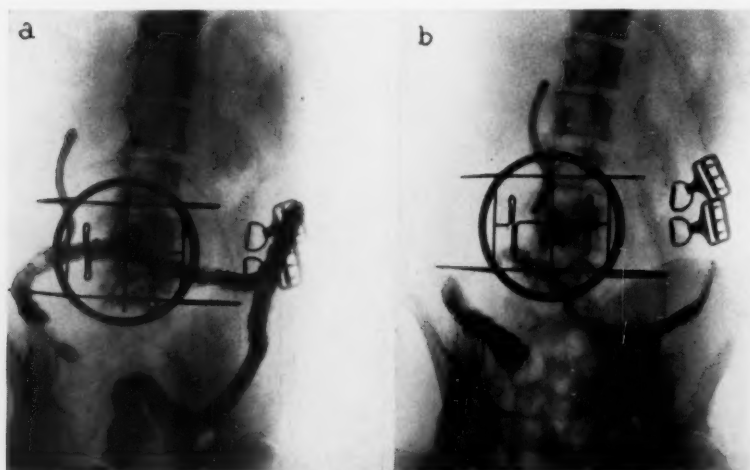


FIG. 5.—Case 8: *a*. The full barium enema taken 18 months after ileostomy. There is foreshortening of the colon with both flexures drawn downward, with little flexibility or distensibility. The mucosal outline is irregular.
b. The empty film shows rapid emptying of the distal half of the colon with retention of barium in the proximal colon. This is an unfavorable case for closure.

RESULTS

There was no operative mortality in this group. The fact that restoration of their intestinal tract was accomplished by anastomosing normal ileum and not any part of the bowel involved with ulcerative colitis is, we believe, responsible for the fact that these cases were closed without complications or mortality.

The results of ileostomy in this group of seriously ill patients were good. In other words, clinical remission was obtained or the symptoms for which ileostomy was elected, were relieved in all nine patients. However, when the ileostomies were disconnected, the results were by no means as satisfactory. Two patients have had complete relief of their disease. One of these was a patient who was operated upon for hemorrhage (Case 3), and the other was a patient who had pelvic peritonitis from a subacute perforation (Case 4). Three patients had a mild recurrence on one occasion and with further

TREATMENT OF ILEOSTOMY STOMA

FIG. 6.

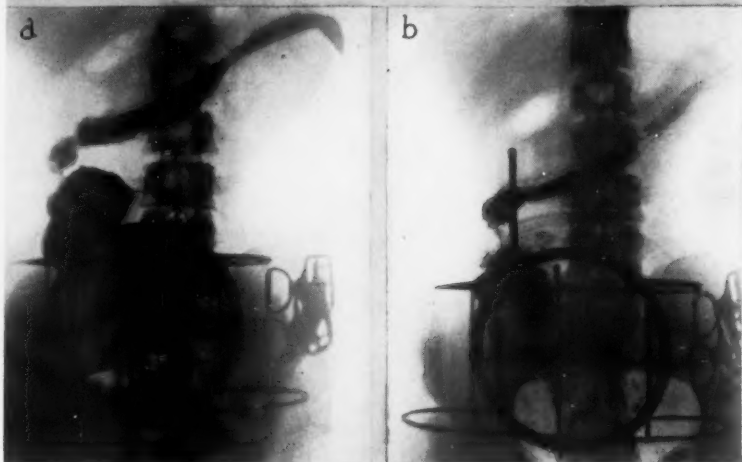
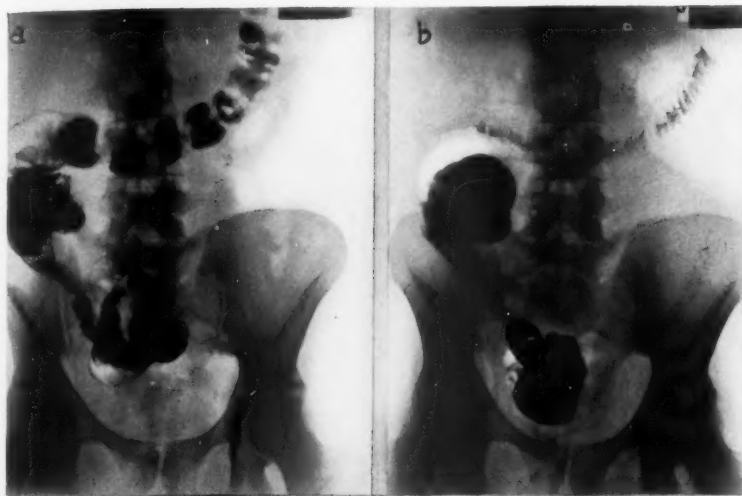


FIG. 7.

FIG. 6.—Case 9: *a* and *b*. The full and empty barium enema taken July 1, 1940, after a modified Mikulicz resection of the ileum and a portion of the right colon for regional ileitis. There is no evidence of ulcerative colitis at this time.

FIG. 7.—Case 9: *a* and *b*. The full and empty enema taken October 5, 1941, 13 months after ileostomy. There is marked contraction, foreshortening, irregular mucosal outline, and rapid emptying. This is an unfavorable case for closure and required a second ileostomy.

medical treatment have remained well (Cases 1, 2 and 5). We consider these five patients to have a satisfactory result. Two patients have continuing bowel symptoms without recurrence of fever, but are able to work (Cases 6 and 8). Both of these patients should be considered to be unimproved so far as ileostomy closure goes. Probably ileostomy was responsible for obtaining their clinical remission, but because of cicatricial changes in the colon (Fig. 5), they have mild, obstructive symptoms or have frequent bowel movements daily. Two patients had complete failures and have had

a new ileostomy performed. One of these had had the disease for three years, and the ileostomy was kept open for 28 months (Case 7). The other patient had had trouble for six years, and the ileostomy was kept open for 14 months (Case 9). One failed because of definite obstruction and malnutrition, without evidence of active infection, while the other failed because of definite recurrence of ulcerative colitis.

A consideration of these cases demonstrates clearly that the best results can be anticipated in those patients in whom ileostomy has been done relatively early, since the favorable results in this group of nine patients were clearly in a group of cases in which early ileostomy was decided upon. A patient, recently operated upon, demonstrates this quite well. She had been observed for a period of two years, during which time she has had two long periods of medical treatment in the hospital. The barium enema at the time of the initial treatment (Fig. 8 *a*) shows an enlarged, dilated colon, with a smooth outline. After evacuation of the enema, spasm and contraction were seen in the distal half of the colon, with satisfactory haustral markings in the proximal two-thirds of the colon (Fig. 8 *b*). Two years later, when she had very unsatisfactory results from medical treatment, the barium enema showed marked contraction and foreshortening of the colon, with both splenic and hepatic flexures drawn downward. There were no haustral markings either before or after the enema and the mucosal pattern was definitely irregular (Fig. 9 *a* and *b*). Since we did not elect ileostomy two years ago, we have lost any chance of restoring continuity in this patient. Ileostomy was performed March 24, 1942. There will be further contraction to produce the typical "lead-pipe colon" in this patient within three to six months after ileostomy. If she still continues to have symptoms, total colectomy will be necessary. The clinical story and roentgenograms in this patient demonstrate clearly our reasons for recommending early ileostomy in serious cases of ulcerative colitis.

Any patient who is not doing well on medical treatment, continuing to lose weight, run fever, and with excessive stools, should have ileostomy. Patients with the acute, fulminating form of the disease who do not respond to medical management within the first five to seven days should have ileostomy. In the acute, fulminating cases ileostomy should be done in all of them whether it is the first attack or a recurrent acute attack, unless they have a rapid response to treatment. In our group of nine patients, closure of ileostomy was possible in patients who were done as recommended. We believe in spite of a limited experience that definite evidence has been presented to show that closure of ileostomy can be done in specially selected cases where ileostomy has been done reasonably early. Approximately 25 per cent of all cases of ulcerative colitis will require surgical treatment. Closure seems possible in approximately 10 per cent of operated cases. If the indications for ileostomy are extended and if ileostomy is decided upon earlier, this figure may be increased.

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FIG. 8.

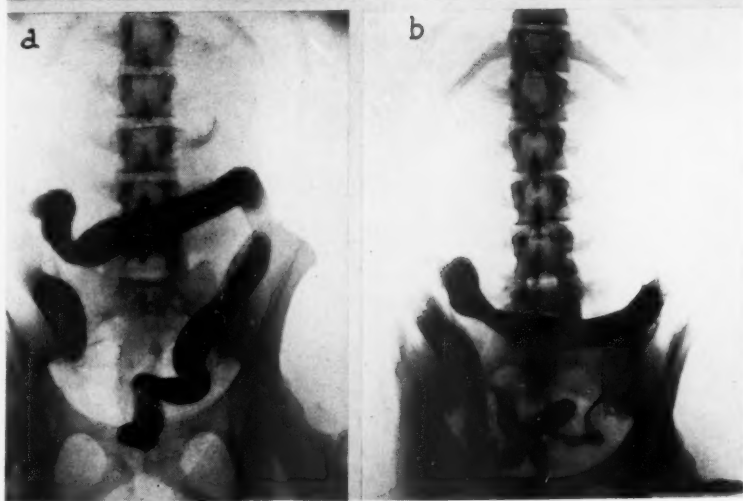
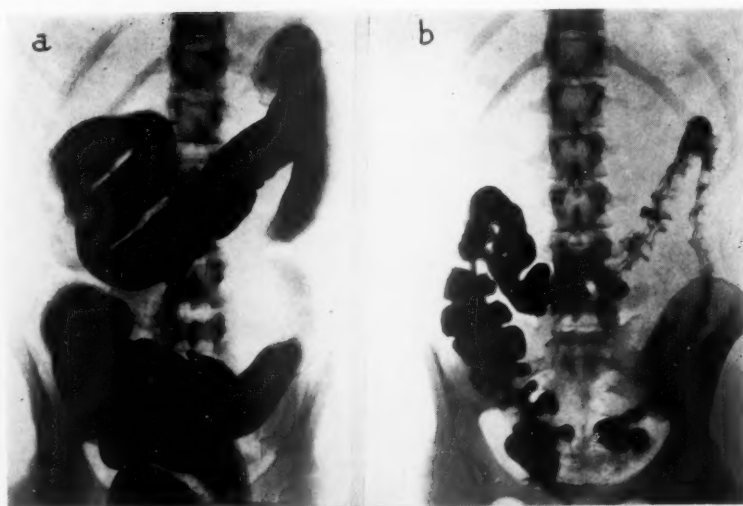


FIG. 9.

FIG. 8.—*a*. The full enema of the colon of a young woman with a severe, first, acute attack of ulcerative colitis. The outline of the mucosa is smooth, with a suggestion of haustral markings. There is no contraction.

b. With the empty film there is excessive emptying of the distal half, with retention of barium in the proximal half of the colon. This is the ideal roentgenogram finding for early ileostomy with a chance of subsequent closure.

FIG. 9.—*a* and *b*. After recurring, acute attacks and several periods of medical trial utilizing all conservative means, the colon is now foreshortened and contracted, with a smooth outline. Ileostomy was necessary because of medical failure. There is now no prospect of subsequent closure.

SUMMARY AND CONCLUSIONS

The present status of the surgical treatment of ulcerative colitis is reviewed, and the surgical indications for ileostomy are presented.

Closure of ileostomy has been carried out in nine patients, with satisfactory results in five. Two continue to have symptoms sufficient to make

them unsatisfactory, and two were complete failures, and a second ileostomy was required. There were no operative deaths.

Early ileostomy for patients with serious ulcerative colitis is recommended when medical treatment fails, in order to obtain the earliest possible remission before irreversible structural changes in the colon occur. It is in this group that later closure of the ileostomy can be considered.

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DISCUSSION.—DR. HENRY W. CAVE (New York): To condemn an individual, particularly the young, to permanent ileostomy is a serious decision. We all recognize that the mortality after ileostomy is approximately 20 per cent; due to the fact that both the physician and the gastro-enterologist, knowing the disease to be a cyclically recurring one with phases of convalescence and quiescence, hope for a remission. Thus they *wait and wait*, until the call for emergency surgery in desperately ill patients is sent out; after hemorrhage, septic fever, dehydration, and total lack of any type of resistance to infection have taken their toll.

Doctor Cattell, no doubt realizing the profound morbidity of this disease, and the discomfiture of an abdominal fecal fistula is convincing, I feel, in his presentation that early ileostomy is justified; and that in selected cases the ileal stoma can be taken down and fecal continuity restored.

We must be cautious in advising early ileostomy only when it is beyond question that the patient is suffering from a true ulcerative colitis, as we know it, and not from amoebic or bacillary dysentery, or milder form of colitis which is amenable to medical management.

To obtain "the earliest possible remission before irreversible changes have taken place" in severe ulcerative colitis, the earlier the ileostomy the greater the chance of complete permanent restoration of the fecal stream.

Doctor Cattell has been fortunate in having turned over to him six of the nine patients (whom he closed later) with the disease existing for a period not longer than six months. I have had no such luck. All of the 45 patients to whom I have given an ileostomy, except three (who had massive hemorrhages, and who were of the acute, fulminating group, and who died after ileostomy), had irreversible changes before I had been given the opportunity of diverting the fecal flow. I believe that he is right, without question, when he states "that an attempt to restore intestinal continuity by anastomosis of the proximal ileum to a portion of the large intestine involved with ulcerative colitis, either in the infective, infectious or healed stage, should be condemned." Also, I am in complete agreement with his "policy regarding permanent irrevocable ileostomy for advanced cases."

I am not in accord with all of Doctor Cattell's indications for ileostomy in ulcerative colitis—particularly in reference to *massive hemorrhage*. We have had a 50 per cent mortality where we have given ileostomy to patients in the acute, fulminating stage, accompanied by massive hemorrhage. It is my opinion, that the mortality can be lowered considerably, if, by the use of papaverin hydrochloride, belladonna and repeated transfusions, they can be carried through this desperate stage of hemorrhage and converted into a more chronic form.

To me, it is of especial interest to learn of Doctor Cattell's criteria for selection of cases for closure of ileostomy. The first, a clinical remission of symptoms following ileostomy; and that accompanying medical treatment should be maintained for an appreciable period. By this appreciable period, I assume he means from six to eight months

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or even longer, and I should like to ask Doctor Cattell if he has used either sulfalylguanidine or sulfasucidine in irrigating out the colon or has given orally the other sulflylonamides during this waiting period. Secondly, that the inflammatory process must be shown to have healed and to be inactive, as observed by sigmoidoscopic examination. I have found it difficult to determine accurately how inactive the process is by the use of the sigmoidoscope. So many patients seem to be in the quiescent stage and yet the slightest irritation from the insertion of the sigmoidoscope will produce bleeding, and a granular mucosal surface will exist indefinitely. Thirdly, the distensibility of the colon by means of a barium enema or double contrast air enema; and also that the haustral markings should be demonstrable, "at least in the film taken after evacuation of the enema." To me, the presence of haustral markings in the entire colon after evacuation of the enema would indicate a reasonably favorable and successful closure. Needless to say, as he has stated "that if the mucosal pattern shows a pseudopolypoid or a too regular outline, closure would be out of the question." He states that one of the series of nine patients who had the disease for three years was a definite failure after closure and, also, he states that another patient, ill for six years, proved a failure after closure. It seems to me that these two failures should have been expected.

The duration of the medical management before operation was short, "one to seven days, three; one to four weeks, three; one to three months, two; 21 months, one." Ninety per cent of the patients in my own series have been treated for a much longer period. There was no operative mortality in this group of nine that he closed. May I ask what type of ileostomy was carried out? Was it divided or end-ileostomy, or was it a loop-ileostomy? It would seem to me that, particularly in the acute, fulminating type, of which he had one, and of the massive hemorrhage type, of which he had one, that loop-ileostomy would be less hazardous.

In all nine of the patients, ileostomy showed a clinical remission of the disease "but when the ileostomy was disconnected the results were by no means as satisfactory." Two of the patients were complete failures and had to have new ileostomies performed. Even with these failures, I believe that to have had five of the nine patients with satisfactory results justified the procedure of early ileostomy and subsequent closure of the opening.

I wish to congratulate Doctor Cattell in his fine presentation, for I am sure it is a step forward in the treatment of this devastating disease. Ileostomy, at its best, is assuredly undesirable; and any method, program or maneuver that can eliminate it, is to be commended.

DR. WILLIAM E. LADD (Boston, Mass.): I am a little bit in the position that Doctor Oughterson put Doctor Harvey in yesterday, because Doctor Gross is looking up our data at the Children's Hospital on ulcerative colitis, but I have not been permitted to see them yet, so I do not have all the data at hand.

I think we have not felt justified in undertaking an ileostomy quite as early as Doctor Cattell has. In children it is, I think, fairly difficult to group the cases into the ones that may possibly recover as the result of prolonged medical treatment and the cases that will never recover as a result of prolonged medical treatment. So we have not felt quite justified in performing ileostomy as early as some of Doctor Cattell's cases. However, I think we have established them perhaps earlier than some others have.

We have had seven cases which we have closed after leaving the ileostomy functioning for quite a long period of time. I think a good deal longer period of time than Doctor Cattell has used. I do not think we have closed any prior to the ileostomy having functioned for at least two years. I think that these seven cases that have been closed have all remained well. I know that in one case I closed 12 years ago. I had a letter from the patient two or three weeks ago, saying that she was perfectly well and asking whether we thought it was advisable for her to get married, having had her previous history. I advised her to get married, and I presume she has.

There is one unfortunate case which we had, that I think perhaps is quite as important as the clinical observation on the cases that we have closed. This case was a boy of about six, who had an ileostomy, which had been open for about two years. I had examined him by the sigmoidoscope, and I thought he was a suitable case for closure, and I had made an appointment for him to come into the hospital to have it undertaken. In the interim, he developed a volvulus from which he died. We had a postmortem examination, and a very careful examination of the colon showed it to be completely healed. It seems to me that this is really a very important piece of data.

Now I think there may be some of you who are not familiar with the fact that this

disease occurs in very early life at times. We have had three cases in the first six months of life. Of these, one had an ileostomy which was closed, and I think that was about three years ago. That child is quite all right. One has had an ileostomy, and on frequent examinations we have not felt justified in closing it, as there is still evidence of the disease persisting in the colon. The third was kept on our medical ward and was not correctly diagnosed by our medical colleagues, and died. The postmortem examination showed a typical ulcerative colitis, with perforation, and death from peritonitis.

DR. FRANK K. BOLAND (Atlanta, Ga.): I would not rise again, except for the reference which was made to what I said about ulcerative colitis in the Negro.

It is true that the colored race had very few cases of this condition. As a matter of fact, I have seen only two or three in a long period of time. But I am familiar with two cases of ulcerative colitis which apparently were cured by one of the sulfonamide drugs, called by our friend, Doctor Gage, "sulfa-cure-all drugs." That seems to be a good name. I did not think that was so important, but when I heard from one of the most eminent colon surgeons in our country that the use of these drugs had almost eliminated the necessity for operation, I felt that something new was here, and that is the reason it was mentioned in the paper.

I would like to say, in this connection, a word about these drugs. I think there are two things which should be considered in evaluating a drug or any procedure, and that is not only the number of cases in which you have used it but also the length of time which has elapsed since the procedure came into use.

For instance, you all recall how enthusiastic we were in World War I about the use of the Carrel-Dakin treatment. We thought that was fine, and it did seem to be fine. But I heard some gentlemen recently, who had treated and seen some of the patients at San Francisco who had come from Pearl Harbor, tell the valuable, wonderful results of sulfathiazole treatment of wounds. Several of them seemed to think: "We will not have to use that Carrel-Dakin treatment any longer." I hope they will not be saying that 20 years from now about the wonderful drugs we seem to have to-day.

Our President is very fond of telling a story to drive home a point, and I have a little story I think illustrates the error of drawing conclusions from too small a series of cases. In the days of typhoid fever, when we had perforations and hemorrhage, a young physician had in the ward an Irishman who was in a very low state of typhoid fever, and it seemed that he was going to die. As you remember, the patient with typhoid fever was not fed anything in those days. This Irishman was very hungry. Seeing a big plate of cabbage on the table between him and another patient, he reached over and took it and ate all the cabbage. The young doctor knew his patient was gone, but strange to say, the patient immediately got well.

A little later the same young physician had a Swede in the ward with typhoid fever, and he reached about the same condition the Irishman had been in. Remembering the luck he had had with the Irishman's eating cabbage, he gave this Swede some cabbage, and the Swede immediately died.

Then the young doctor wrote a paper on the use of cabbage in the treatment of typhoid fever, and his conclusions were that cabbage in typhoid in an Irishman was a wonderful thing, but in a Swede it was not worth a damn.

DR. RICHARD B. CATTELL (closing): I appreciate the discussion, including Doctor Boland's reply. I think I might comment on it first and say that I think his caution with regard to any interpretation of results in a small series of cases, such as this, certainly must be approached with great prudence.

Dr. Cave raised the question with regard to hemorrhage and how serious these cases are. We feel that only ileostomy offers any possible prospect of surgical help in these cases. We have employed actual irrigations with sulfonamides in only a few. We have used sulfanilguanidine and other sulfonamides by mouth, and our results, chiefly done under Doctor Kiefer's direction, have not been as satisfactory as many that have been reported.

With regard to the other question of Doctor Cave, as to the type of ileostomy, we have established a divided ileostomy in all of these cases.

In the text of my paper you will find the reference to Doctor Ladd's and Doctor Gross's series of closures in seven children. I was familiar with this work, and I think that it was largely instrumental in encouraging us to try this in adults. I think Doctor Ladd's results are better than our own. I believe that one of the reasons why the percentage of our number of recurrences is high is because we tried it in bad as well as in good cases.

EXPERIENCES WITH THE SURGICAL MANAGEMENT OF DIVERTICULITIS OF THE SIGMOID*

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A SURVEY of the literature and of experiences with the management of diverticulitis of the colon at the Massachusetts General Hospital during the past 15 years indicates that this is a comparatively rare disease. It is the result of inflammation in and about outpocketings from the bowel. These most frequently appear to consist of mucosal pouches which protrude through the muscularis, presumably the result of pressure from within, probably acting in conjunction with some congenital defect in the muscular layer (Mayo, Wilson, and Griffin [1907]). This condition, known as diverticulosis, is rare, for Rankin and Brown (1930) found evidence of it in 0.3 per cent of 765,795 patients subjected to roentgenologic examination. Time is apparently an important factor, for if the age of the patient is taken into consideration, it would appear that approximately 5 per cent of people who are age 40 or over will have diverticulosis (Brown [1939]). It is not surprising, therefore, to find that diverticulitis is rare in the younger age-groups. It begins to make its appearance in the fourth decade of life and is maximal in the sixth (Table I). It is also apparent that males are affected more commonly than

TABLE I
DIVERTICULITIS

Age	No. of Cases*
20-29.....	1
30-39.....	24
40-49.....	86
50-59.....	131
60-69.....	105
70-79.....	19
80-89.....	3
Total.....	369

* Graham (1937), Brown (1939), Eggers (1941), and M. G. H. (1942).

females, the ratio being 1.6 to 1. This is particularly apparent in those patients who develop spontaneous bladder fistulae, where the ratio of males to females increases to 8.5 to 1 (Table VI).

The distribution of diverticula in the colon is of interest, as this has a bearing upon surgical complications. It is apparent that the sigmoid is involved more frequently than any other segment of the large bowel and the rectum least frequently. The sigmoid contains diverticula in 75 per cent of cases,† and the rectum in 2.4 per cent. Between the sigmoid and the cecum,

* Read before the American Surgical Association, Cleveland, Ohio, April 6-8, 1942.

† Spriggs and Marxer (1927), and Brown and Marcle (1937).

the incidence of diverticula in the various segments of the colon decreases steadily. All segments of the bowel are occasionally involved (14.4 per cent). One might, therefore, expect that, on the law of chances, surgical complications would occur most frequently in the sigmoid. This appears to be the case, in fact, they rarely occur in any other segment. During the 15-year period, in which the 64 cases included in this report were operated upon for diverticulitis of the sigmoid, there were only two other cases subjected to surgery for complications of diverticula in other portions of the colon. One involved the cecum, and the other the ascending colon. In the latter instance, actinomycosis was also present. D. F. Jones (1930) stated that he had seen but one surgical complication of diverticulosis above the upper end of the sigmoid and that was in the cecum. This indicates that other factors which affect the sigmoid in particular, such as a narrow lumen, stasis, and solid fecal material may be important.

The sigmoid is also the most frequent site of carcinoma of the colon. Allen and Welch (1939) found that in a series of 634 carcinomata of the large bowel, not including the rectum, the lesion was situated in the sigmoid in 53.9 per cent. This probably is the reason why there is an association between diverticulitis and cancer, rather than that the former favors the occurrence of the latter. This appears to be the conclusion of most who have commented upon this matter in the more recent literature, Abel (1935), Brown and Marcle (1937). Certain statistical data also supports this viewpoint, as Rankin and Brown (1930) found diverticula associated with cancer in only four of 679 carcinomata of the bowel, an incidence of 0.6 per cent, and cancer associated with diverticulitis in four of 227 cases, an incidence of 1.8 per cent. The latter figure is lower than that reported by Eggers (1941), who found the incidence to be 6.1 per cent. On the other hand, this figure was less than the incidence of carcinoma of the sigmoid detected in a series of 428 consecutive barium enemata, which Eggers (1941) found to be 7.2 per cent. In this same series of roentgenologic examinations, the incidence of diverticulitis was 4.2 per cent.

The differential diagnosis between diverticulitis and cancer has been a topic for some discussion, particularly with regard to bleeding as a symptom and the value of roentgenograms as a diagnostic aid. Considerable evidence is available upon the former question, and indicates that a history of bleeding was present in 15.7 per cent of 568 patients* known to have diverticulitis. Of 309 cases† known to have diverticulitis in which the incidence of cancer and bleeding were both recorded, the incidence of cancer was 2.9 per cent, and of bleeding 16.5 per cent. With regard to the value of the roentgen ray in differentiating between the two lesions, Schatzki (1940) stated that the differential diagnosis is easy in most, difficult in some, and impossible in a few cases. Because of the fact that the symptoms, the signs, the age of the patient, the area

* Judd and Pollock (1924), Spriggs and Marxer (1927), Rankin and Brown (1930), Ochsner and Barger (1935), Eggers (1941), and M. G. H. (1942).

† Rankin and Brown (1930), and Eggers (1941).

DIVERTICULITIS OF SIGMOID

of the bowel involved, the roentgenologic findings, and the gross appearance of the lesion at operation may be quite similar, it seems clear that excision of the involved segment of the bowel is the only certain answer to this question. This was the reason for resection of the sigmoid in eight (24.2 per cent) of the 33 cases included in this report. No case in which cancer and diverticulitis were associated in the same segment of the bowel is included in this series. In one case, a small, low, nonobstructing carcinoma of the rectum was present, and is included because it was felt that it had no obvious connection with the perforated sigmoid with abscess formation. Benign polypi were found in two of the 33 resected specimens.

The question arises as to how frequently patients with diverticulosis of the sigmoid develop diverticulitis. Some statistical data bearing upon this point indicates that roentgenologic evidence of diverticulitis was present in 25.1 per cent of 2,400 cases* having diverticulosis. Brown (1939) believes that as many patients with diverticulosis probably have mild attacks of diverticulitis and are not roentgenographed, that a more likely estimate would be 10 per cent. It is likewise impossible to estimate accurately the number of patients with diverticulitis who require surgical intervention. From reports in the literature dealing with both the medical and surgical management of this lesion, it was found that 28.5 per cent of 1,332 cases† coming under observation were operated upon for one reason or another. Here again, this figure is probably too high and it would seem more likely that about 10 per cent of all cases of diverticulitis require operation. This is in keeping with the experiences of Brown and Marcley (1937) with the medical management of this disease, in which they state that the results were found to be satisfactory in 63 per cent of their cases and adequate in three-quarters of the remaining 37 per cent, which implies an unmanageable situation in 9.3 per cent of patients with diverticulitis. During the 15-year period which this report covers, our own experience indicates that of all patients hospitalized for diverticulitis, 64 (19.2 per cent) were treated surgically and 269 (80.8 per cent) were treated medically. Undoubtedly, there were many more cases treated medically without hospitalization. To summarize this matter briefly, it would appear that about 5 per cent of people over 40 years of age have diverticulosis. Graham (1937) has estimated that this means about 12 in 250 patients over 40 will have diverticulosis and one in 250 will have diverticulitis. If we assume that one in ten cases with diverticulitis will require operation, this means that a surgical problem will arise in approximately one in 2,500 people over 40 years of age. It is apparent that the experience of most surgeons with this disease cannot be great, and it is not surprising that the literature dealing with the results of various operations is not extensive.

* Rankin and Brown (1930), and Brown and Marcley (1937).

† Spriggs and Marxer (1937), Rankin and Brown (1930), Brown and Marcley (1937), Stetten and Abeloff (1938), Lockhart-Mummery (1938), Eggers (1941), and M. G. H. (1942).

TABLE II
MANIFESTATIONS OF DIVERTICULITIS*

	No. of Cases	Perforation	Per Cent
(a) Incidence acute perforation.....	545	73	13.4
(b) Incidence abscess.....	506	60	11.9
(c) Spontaneous bladder fistula.....	611	80	13.1
(d) Various other lesions			38.4
Acute	} nonperforated.....		61.6
Subacute			
Recurrent			
Chronic			
			100.0

* Judd and Pollock (1924), Rankin and Brown (1930), Graham (1937), Brown and Marcle (1937), Lockhart-Mummery (1938), Brown (1939), Eggers (1941), and M. G. H. (1942).

It is apparent (Table II) that nearly 40 per cent of the patients who come to operation for diverticulitis have either an acute perforation, an abscess, or a spontaneous bladder fistula. The incidence of these three complications appears to be about the same. An occasional case may have fistulae into other intestinal loops. About 60 per cent are operated upon for various other lesions, largely nonperforated or not obviously perforated. In many instances, the preoperative diagnosis is incorrect, and was so in 29 (45.3 per cent) of our 64 cases. Appendicitis, intestinal obstruction, carcinoma, and pelvic tumors were the more common mistakes. It is of interest that the symptoms in the majority of 156 cases* were of short duration, less than a month in 25 per cent, less than a year in 66.6 per cent, and less than five years in 91 per cent. This has been emphasized by Brown (1939). In our series, it was found that the first attack was severe and required operation in 48 per cent of the cases. The implication is that in cases which come to operation the disease is unusually severe or persistent.

TABLE III
MORTALITY STATISTICS*

	No. of Cases	Deaths	Per Cent
(a) Acute perforation—principally drainage \pm suture.....	42	10	23.7
(b) Abscesses—incision and drainage.....	43	4	9.3
(c) Bladder fistula—various operations.....	53	10	18.9
(d) Various lesions—various operations not including resection but including colostomy.....	173	17	9.8
(e) Various lesions—resection of sigmoid—all technics.....	181	31	17.1†

* Graham (1937), Brown and Marcle (1937), Lockhart-Mummery (1938), Brown (1939), Eggers (1941), and M. G. H. (1942).

† Mortality of various types of resection (25.0–6.1 per cent).

The immediate mortality is variable (Table III) and depends upon the nature of the lesion and the type of operation performed. It was 23.7 per cent for acute perforations, 9.3 per cent for abscesses, and 18.9 per cent for bladder fistulae. The mortality for various operations including colostomy, appendectomy, exploratory celiotomy, cecostomy, and miscellaneous maneuvers for various lesions was 9.8 per cent. The mortality for resection by all technics for various lesions was 17.1 per cent. This has been emphasized by

* Total of Brown (1939), and M. G. H. (1942).

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Laufman (1941). The mortality for resections by certain technics (Table IV) varied, and was 11.5 per cent for Mikulicz resections, 17.3 per cent for resection with anastomosis following preliminary colostomy, 20 per cent for obstructive resections, and 26.3 per cent for one-stage resection with anastomosis.

TABLE IV
RESECTION BY CERTAIN TECHNICS*

Technics	No. of Cases	Deaths	Mortality
(1) Mikulicz resection. Later close colostomy.....	61	7	11.5%
(2) Preliminary colostomy. Subsequent resection, with anastomosis. Later close colostomy.....	52	9	17.3%
(3) Obstructive resection. Later close colostomy.....	20	4	20.0%
(4) One-stage resection. With anastomosis.....	19	5	26.3%
Total.....	152	25	16.4%

* Brown and Marcle (1937), Brown (1939), and M. G. H. (1942).

TABLE V
LATE RESULTS—VARIOUS LESIONS

	No. of Cases	Living and Well	Living, Not Well	Subsequent Death from Disease	Subsequent Death Other Cause	Unknown
(a) Various operations other than colostomy or resection*.....	98	45 (45.9%)	33 (33.7%)	8 (8.2%)	8 (8.2%)	4 (4%)
(b) Colostomy*.....	78	49 (62.8%)	12 (15.3%)	7 (9%)	8 (10.2%)	2 (2.6%)
(c) Close colostomy*.....	36	19 (52.8%)	14 (38.9%)	3 (8.3%)
(d) Resections†.....	109	83 (76.1%)	8 (7.4%)	4 (3.7%)	8 (7.4%)	6 (5.4%)

* Brown and Marcle (1937), Lockhart-Mummery (1938), Brown (1939), Eggers (1941), and M. G. H. (1942).

† Lockhart-Mummery (1938), Brown (1939), and M. G. H. (1942).

The late results (Table V) and mortality following various operations, such as exploratory celiotomy, appendectomy, with or without drainage, and miscellaneous operations, not including colostomy or resection for various lesions, including patients surviving suture and drainage of acute perforations and drainage of abscesses, have been collected from the literature in 98 cases. Of these, 45.9 per cent are living and well, and 33.7 per cent living and not well. The late results of proximal colostomy are given for 78 cases, of which 62.8 per cent are living and well, and 15.3 per cent living and not well. These results appear to be better as far as relief of symptoms are concerned, but the late mortality of the disease was not significantly altered being 8 to 9 per cent in each group. It is of interest to note that colostomies were closed in 36 cases. This was unsuccessful in 47.2 per cent of cases. The late results of resections of the sigmoid indicate that this is a more effective form of treatment. Of 109 cases, 76.1 per cent were well, 7.4 per cent not well, and the late mortality from the disease was 3.7 per cent.

One of the more distressing complications is the bladder fistula (Table VI). This occurs primarily in males and has already been commented upon. Certain operations, particularly direct attempts to close the fistula have not met with much success. Colostomy has been helpful, resection appears to be more effective.

TABLE VI
BLADDER FISTULA

	No. of Cases	Males	Females	
(a) Sex incidence				
Brown (1939).....	30	27	3	
M. G. H. (1942).....	8	7	1*	
	38	34 or 8.5	4 1	
(b) Sex incidence diverticulitis†.....	535	333 or 1.6	202 1	
				Subsequent Death from Disease
(c) Late results miscellaneous operations	No. of Cases	Living and Well	Not Well	
Brown (1939).....	10	0	6	4
M. G. H. (1942).....	1	0	1	0
	11‡	0	7	4
(d) Late results proximal colostomy				
Brown (1939).....	1	1	—	—
M. G. H. (1942).....	4	1	2	1
	5	2	2	1
(e) Late results resection sigmoid				
Brown (1939).....	12	12	—	—
M. G. H. (1942).....	3	3	—	—
	15	15	0	0

*Previous total hysterectomy

†Judd and Pollock (1924), Stetten and Abeloff (1938), Lockhart-Mummery (1938), Brown (1939), and M. G. H. (1942).

‡Close fistula five cases

The immediate and late results of all operations, excepting resection, which were performed in 42 cases of diverticulitis are summarized in Table VII. There were four cases with acute perforation, nine with abscesses, three with bladder fistulae, and five with acute diverticulitis and early peritonitis, simulating appendicitis. The remaining 21 cases had various lesions which were less acute to chronic in nature. A mass was present in all at operation. These were nonperforated or not obviously perforated lesions. Large bowel obstruction was present in five. There were two deaths (4.8 per cent), both from general peritonitis, one following drainage of an abscess, and one following suture and drainage of an acute perforation. There were 13 immediate complications. Seven cases developed fecal fistulae, two general peritonitis, in one, a bladder fistula recurred six days after closure. One case developed major wound sepsis with separation, and one developed small intestinal obstruction.

The late result is known in the 40 surviving cases. Sixteen (40 per cent) are classed as well. Of these, six had proximal colostomies, and one, an entero-enterostomy between the transverse colon and the sigmoid distal to the lesion. The colostomy was closed in two cases. The symptoms recurred in both. No further surgery has as yet been necessary. Of the remaining nine cases in this group, three have subsequently died of other causes, two years eight

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TABLE VII

VARIOUS OPERATIONS—M. G. H. (1942)—42 CASES

Excepting Resection—Arranged According to the Lesion

Lesion	Immediate Result				Late Result			Subse- quent Death —Dis- ease
	No. of Cases	Operation	Compli- cations	Deaths	No. of Cases	Living and Well*	Not Well†	
Acute perforation.....	4	Suture and drain	2	1	3	2	1	—
Abscess.....	9	I. and D.	6	1	8	2	5	1
Bladder fistula.....	3	Prox. col. (2) Close fist. (1)	1	0	3	1	1	1
Acute diverticulitis.....	5	Append. with drain (4)	3	0	5	1	4	0
Acute Subacute Chronic	2	Exp. celiotomy Colos.	0	0	2	0	2	0
	4	Exp. celiotomy Biopsy Exc. T and O. Enter'ty	0	0	4	2	2	0
	7	Exp. celiotomy Colos.	1	0	7	5	1	1
	3	Exp. celiotomy Cecostomy	0	0	3	1	1	1
	5	Cecostomy Obstructed	0	0	5	2	2	1
	42		13 (30.9%)	2 (4.8%)	40	16 (40%)	19 (47.5%)	5 (12.5%)

* Two subsequent deaths, unrelated cause.

† One subsequent death, cause unknown.

months; 5 years seven months; and seven years two months after operation. Six are living and well, from seven months to 14 years after operation.

Nineteen cases (47.5 per cent) were classed as not well. Of these, 15 (78.9 per cent) have required further operation either for persistent symptoms or disease or for recurrent disease. In 11, resection was necessary. Three cases are living from two years six months to five years after operation, with persistent symptoms or recurrent attacks for which no further surgery has as yet been necessary. One patient died one year 11 months following proximal colostomy for bladder fistula. Until then his urinary tract infection persisted. The exact cause of death is not known.

Five cases (12.5 per cent) subsequently died of their disease. In one case, a bladder fistula, multiple operations were performed, including a terminal ileostomy. The patient eventually died of urinary tract sepsis and uremia, seven years six months after onset. One case died two years after cecostomy of a recurrence of his disease, further surgery being performed elsewhere. One case died elsewhere, six months after proximal colostomy of persistent sepsis. Two patients did well for six years and eight years six months after operation, and then died of recurrent disease. In one, a further operation for drainage of a recurrent abscess was performed, and death was due to general peritonitis.

A study of these results indicates that the outlook for patients with severe forms of diverticulitis is not very bright. The majority have not done well.

The sigmoid was resected in 33 cases. Eleven had had previous operations as described in Table VII. This makes the total series 64 cases. The immediate and late results are given in Table VIII. Six cases which were followed for less than one year were eliminated from the tabulation of late results. The average follow-up for the remaining 25 cases was four years six months. Fifteen cases have been followed for from one to five years, and nine for from five to ten years. The result in one case operated upon six years six months ago is unknown.

TABLE VIII
RESECTION SIGMOID (M. G. H. 1942)—33 CASES

Lesion	Arranged According to the Lesion			Late Result (1-10 Yrs.)				
	Immediate Result							
	No. of Cases	Complications	Deaths	No. of Cases	Living and Well*	Not Well	Subsequent Death—Disease	Unknown
Recurrent diver'tis, with mass	9	3	0	8	7	1	0	0
Recurrent diver'tis, without mass, with thickened mesentery.....	3	0	0	3	1	2	0	0
Chronic diver'tis, with mass, ? ca.....	8	5	2	5	4	0	0	1
Bladder fistula.....	4	2	0	3	3	0	0	0
Persistent ext. fistula.....	4	1	0	2	2	0	0	0
Acute diver'tis, with mass....	2	0	0	2	2	0	0	0
Acute diver'tis, with abscess.	2	0	0	1	1	0	0	0
Subacute and chronic diver'tis, with persistent obs.....	1	0	0	1	1	0	0	0
	33	11	2	25	21	3	0	1
		(33.3%)	(6.1%)		(84%)	(12%)	(0%)	(4%)

* Two subsequent deaths, unrelated cause.

Twelve cases were resected because of recurrent attacks of diverticulitis, eight because of chronic diverticulitis with a mass simulating carcinoma, eight because of persistent fistulae, four had acute lesions with an associated abscess in two instances, and one case had persistent obstruction due to a fibrostenosing lesion.

There were two deaths, a mortality of 6.1 per cent. There were 11 complications (33.3 per cent). Of the 25 cases included in the tabulation of late results, 21 (84 per cent) are classed as well, three (12 per cent) as not well. There have been no subsequent deaths from the disease. The result in one case is unknown. Of the 21 cases classed as well, two have subsequently died of other causes, one of a cardiac lesion four years six months later and the other committed suicide one year after operation. Until then there were no difficulties due to diverticulitis, although it appears that the many operations which had been performed upon the patient who committed suicide probably contributed to his depressed state of mind. On the whole, the results in this group of resections are encouraging, and the impression gathered from a study of these cases suggests that this form of treatment appears to offer the patient

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suffering from a severe form of diverticulitis the greatest hope for relief and appears to lessen the subsequent mortality from the disease.

TABLE IX
RESECTION OF SIGMOID—EARLY RESULTS

(1) Exteriorizing Operations—15 Cases

Immediate Complications

Technic	No. of Cases	Number	Nature	Deaths	No. of Cases	
(a) Proximal loop only. Anterior resection with closure distal stump. Drainage 2, No drainage 2, Proximal colostomy 2, Primary resection 2	4	4	Gen'l perit'itis, retro-peritoneal sepsis, 2 Fecal fistula, small bowel obs., 1 Gangrene colostomy, small bowel obs., 1	2 0 0	C	D
					4	2
					100%	50%
(b) Both loops. Mikulicz 10, loops separated 1. Primary resection 9 (Alone 4, with cecostomy 5), preliminary cecostomy or colostomy 2	11	3	Small bowel obs., 3	0	No. of Cases	
					11	
					C	D
					3	0
					27.3%	0%
	15	7		2		
		(46.7%)		(13.3%)		

(2) Resection with Immediate Anastomosis—18 Cases

				No. of Cases	
(a) Aseptic end-to-end anastomosis. Prel. cecostomy 3, accompanying cecomy 3.....	6	2	Serious leakage suture line, abscess, ext. fistulae, 2	0	6
					C D
					2 0
					33.3% 0%
				No. of Cases	
(b) Preliminary transverse colostomy. Aseptic end-to-end 6, aseptic lateral 1.....	7	1	Leakage suture line, local abscess, 1	0	12
					C D
					2 0
					16.7% 0%
				No. of Cases	
(c) Preliminary transverse colostomy. Open end-to-end.....	5	1	Leakage suture line, local abscess, 1	0	6
					C D
					2 0
					16.7% 0%
				No. of Cases	
	18	4		0	22
		(22.2%)		(0%)	
Total for all groups.....	33	11		2	33
		(33.3%)		(6.1%)	

An attempt has been made to determine what factors play a rôle in the immediate mortality, the immediate complications, and why the late results in certain cases were not satisfactory. First of all, it would appear that the technic of resection is a factor. Data bearing upon this point are presented in Table IX. In this, the cases are divided according to the technic employed. Fifteen exteriorizing procedures are contrasted with 18 resections with immediate anastomosis. All the deaths occurred in the former group, and the complications were over twice as frequent. If, however, one divides the exteriorizing operations into two groups, it is apparent that in the first, consisting of four cases in which the proximal loop only was exteriorized and the distal loop closed, all the deaths and the majority of the complications occurred. In the second group (11 cases) in which both loops were brought out by the Mikulicz technic, with one exception, there were no deaths, but small bowel obstruction occurred in three cases. In the first group with the closed distal

loop, fatal general peritonitis and retroperitoneal sepsis occurred in two cases. In the other two, a persistent fecal fistula leading to the distal loop and small bowel obstruction for which multiple subsequent operations have been performed occurred in one, and in the other small bowel obstruction and gangrene of the colostomy resulted, necessitating further operative procedures both immediately and later. It is also of interest that in two of the four cases in this group a preliminary proximal colostomy had been performed eight and nine months previously. In both groups, intestinal obstruction occurred. This complication appears to be characteristic of exteriorizing procedures. It is possible that infection and inadequate peritonealization are factors because this technic is often employed when resecting acute and subacutely inflamed lesions.

The 18 resections with anastomosis may be divided into two main groups, first those with preliminary or accompanying cecostomy. Two of six cases with aseptic end-to-end anastomosis developed leakage at the suture line, extensive sepsis, and abscess formation. Multiple subsequent operations necessitated long hospitalization. In both, this was a near fatal complication. It would appear that neither preliminary nor accompanying cecostomy is adequate protection for this type of anastomosis performed for an inflammatory lesion. The other group consists of 12 cases with preliminary proximal colostomy. Either aseptic or open end-to-end suture was performed in 11. There was one aseptic lateral anastomosis. The same complication occurred in two cases. Of these, one had an aseptic and the other an open end-to-end anastomosis. This indicates that leakage may follow end-to-end suture whether open or closed, whether immediate or delayed. On the other hand, when proximal colostomy preceded resection this complication was not recognized clinically, but only because postoperative roentgenograms happened to be taken. In one instance, the perforation closed in one month and in the other, it practically closed in the same period of time. This demonstrates one advantage of preliminary proximal colostomy. It would appear that the Mikulicz resection or immediate anastomosis preceded by proximal colostomy are comparable as far as low mortality and similar incidence of complications are concerned. In the former, small bowel obstruction was the problem, in the latter it was leakage at the suture line with localized abscess formation. A review of the operative notes in 18 cases with immediate anastomosis and four cases in which anterior resection was performed, indicates that the Mikulicz technic could not have been used in 12 because the lower portion of the sigmoid loop was primarily involved. There probably were others as well. As it does not appear to be possible to decide with certainty beforehand which technic will be indicated, it would seem best to advocate preliminary proximal colostomy in all cases in which resection of the sigmoid for diverticulitis is to be performed if serious complications are to be reduced to a minimum.

Other possible factors which may have a bearing upon immediate complications and late results should be considered. As judged by the length of bowel removed at operation, it would seem that less extensive resections were

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performed in the group with immediate leakage at the suture line. The group living without symptoms had more extensive resections, the average difference being 4.3 cm. This impression is also gathered from a study of such post-operative roentgenograms as were available. The majority of the patients who had either leakage or who were living with symptoms had end-to-end anastomosis of which six of seven were of the aseptic type. Spasm, delay, and narrowing at the anastomosis were common findings in these groups, and were less frequent in patients living without symptoms. In the latter group, narrowing was present in two of nine cases, and spasm in one. Perhaps the most noteworthy finding was absence of delay at the anastomosis in all of the good results examined roentgenologically. Residual diverticula were usually present after operation in all groups.

The character of the bowel at the time of operation is undoubtedly a factor. A narrow lumen, a thick wall, and acute inflammation all seem important, particularly with regard to end-to-end anastomosis. It is also reasonable to believe that the mortality and immediate complications following the Mikulicz type of resection, comparatively safe as it is as a primary procedure, might be, likewise, reduced by a period of delay. If such is the case, the added time consumed would be amply justified. One of the principal reasons for performing a preliminary proximal colostomy is to allow infection to subside. The period of delay should be dependent upon the time required for this to take place.

A review of the pathologic specimens removed at operation showed that of 14 cases in which primary resections were performed acute inflammatory changes were present in 12. There was a time interval of 11 days to three weeks between cecostomy or transverse colostomy and resection in six cases. Acute diverticulitis was present in four. Seven weeks to three months elapsed between proximal colostomy and resection in four cases. Acute inflammation was present in three of these specimens. The time intervals in five cases between transverse colostomy and resection were three and one-half, five, five, five, and eight months, respectively. There was no evidence of acute inflammation in any of these. This suggests that the time interval should be not less than three months and probably need not be over six months. There was a time interval of six to ten months in four cases with persistent external or bladder fistula, between proximal colostomy and resection. Acute inflammatory changes were present in all. It seems reasonable to believe such would be the case as long as a fistula persisted. The interval in such cases would, therefore, appear to depend more upon the time it takes for such fistula to heal.

In this connection, it was found that external fistulae developed in seven of 17 cases in which drainage was employed in the management of acute perforation (three), abscesses (ten), and acute diverticulitis for which appendectomy and drainage were performed (four). Spontaneous healing occurred in two cases in nine weeks and 11 weeks, respectively. In five cases, the fistulae persisted and were observed for five, five, 17, 19 months, and three

years, respectively. At these times, further surgical procedures were instituted, proximal colostomy followed by resection in three, proximal colostomy only in one, and excision with transverse colostomy in one. In the three cases which were resected, the time intervals between colostomy and resection were four and one-half, five, and six months, respectively. The bowel opening was patent in every case. The external fistula healed in one case (time interval six months). One other case, with a fistula of one week's duration, was resected ten months after proximal colostomy. Both openings of the fistula were still patent. In one case, with proximal colostomy only, for external fistula of three years' duration, the external opening closed promptly. The patient also had a bladder fistula which did not heal, suggesting that the bowel opening was still patent.

No evidence of spontaneous and persistent healing of bladder fistulae was found. Proximal colostomy followed by resection was performed in four cases. The duration of the fistulae at the time of colostomy was two years, six months, four and one-half months, and three months. The time intervals between colostomy and resection were two, nine, three, and nine months, respectively. The bladder opening was closed in the first and fourth, the bowel opening in the fourth only.

Proximal colostomy only was performed in four cases with bladder fistulae. In one of these a terminal ileostomy was performed. The fistulae had been present for one, 15, one, and two months, respectively. In the third case, clinical evidence indicates that the fistula healed promptly and has remained healed for seven and one-half years. In the other three, clinical evidence suggests that the fistulae remained active for 15 months, six and one-quarter years, and six and one-third years, respectively. Two of these cases are dead, the first and third. The latter is known to have died primarily of urinary tract sepsis and uremia, and the other was known to have persistent urinary tract sepsis up to the time of death.

It appears to take not less than three months of proximal decompression by colostomy for evidence of acute inflammation in resected specimens to disappear except in cases in which external or bladder fistulae persist. In these cases, acute infection was invariably present even after ten months of proximal colostomy. External fistulae following drainage operations either healed spontaneously in three or four months or persisted up to three years. Following proximal colostomy, two external fistulae healed promptly or within six months. The bowel opening did not heal in either of these. Following proximal colostomy, three external fistulae persisted, the bowel being open in all at the time of resection four and one-half, five and ten months later. Following proximal colostomy for bladder fistulae, healing occurred within a few months in one case and did not take place in three cases for fifteen months, six years three months, and six years 4 months, respectively. From this, it would appear that a time interval of from three to six months should elapse between proximal colostomy and resection. There appears to be little to be gained in cases without fistulae by a shorter interval except where the

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possibility of carcinoma exists, and little to be gained by a longer delay in patients with external or bladder fistulae which have not healed within this period of time.

The length of the resected segment of bowel was short in the majority of instances. This figure is known in 27 cases, the average for the group being 13.6 cm., or 5.4 inches. In 23 cases (85 per cent), the area removed ranged from seven to 15 cm., averaging 12.3 cm. In only four cases was a longer segment removed, the measurements being 17, 17, 24, and 25 cm. In none was this done because the lesion was unusually extensive. In the first two, the purpose was to remove as much as was readily possible and still restore continuity. In the third, the bowel was unusually redundant, and still is according to postoperative roentgenograms. In the fourth, an anterior resection was performed for a low lesion thought to be carcinoma, the segment removed far exceeding the involved area. These findings confirm the statement of Spriggs and Marxer (1927), that the disease generally involves a localized area of the bowel. The reason why the disease is serious in some cases and not in others does not appear to be because it is more extensive, but rather because there is a more serious and persistent process in a localized segment of the bowel. Continuity of the bowel was reestablished in 27 (81.8 per cent) of the 33 resected cases, and judging by the operative notes, could have been restored in all, with one possible exception. When approached directly in the acute phase, the impression may be gathered that the lesion is extensive, for the inflammatory process in the bowel may reach far beyond the point of origin. When in a quiescent phase, it is generally found to be localized in extent, resectable, with restoration of continuity in the great majority of cases, and higher in location than was expected. The lower third of the sigmoid was principally involved in 12 (36.4 per cent) of 33 cases.

CONCLUSIONS

(1) The late results of operations for diverticulitis, which neither divert the fecal stream nor remove the involved segment of the bowel, were unsatisfactory in over 40 per cent of cases. In these, some further surgical procedure often was necessary.

(2) The late results of proximal colostomy were better. Unsatisfactory results occurred in about 25 per cent of cases subjected to this procedure. This operation does not appear to lower the late mortality due to the disease. It does relieve symptoms. Later closure of the colostomy was unsuccessful in over 45 per cent of cases.

(3) The late results of resection of the involved segment of the bowel were unsuccessful in approximately 12 per cent of cases. This operation appears to lower the late mortality due to the disease.

(4) The immediate mortality for resections has been high, the average being 17.1 per cent. This figure varies considerably (25-6.1 per cent). The immediate complications in our series were frequent (33.3 per cent).

(5) The Mikulicz operation was found to be comparatively safe, although

complicated by small bowel obstruction occasionally. The reported mortality (11.5 per cent) for the operation should be reduced if possible. Both open or aseptic end-to-end anastomosis were complicated by leakage at the suture line and abscess formation. In these, the length of the segment removed was short. Leakage was a serious matter in cases in which a preliminary colostomy had not been performed. Preliminary or accompanying cecostomy was not adequate protection for resection with immediate anastomosis. The late results of the Mikulicz operation and open end-to-end anastomosis were satisfactory. There was no evidence of delay at the anastomosis in these. In three cases with less satisfactory late results, aseptic end-to-end suture was performed. In two of these, delay at the anastomosis was found. In general, as judged by postoperative roentgenologic examination, the more extensive resections were performed in cases with satisfactory late results. Anterior resection with closure of the distal segment was found to be an unsatisfactory technic.

(6) The inflammatory process is generally situated in the sigmoid, and confined to a localized area. Resection with reestablishment of continuity is usually possible. There appears to be no contraindication to removing more than the involved segment of bowel. This should place the point of anastomosis in more favorable territory. It would tend to reduce the number of residual diverticula and perhaps the statistical chance of recurrence. In this connection, it appears desirable to guard against delay at the anastomosis.

(7) It is suggested that a preliminary transverse colostomy be performed in all cases in which resection is contemplated, and that the period of delay before resection be from three to six months.

(8) If resection should for some reason be performed in the acute stage, an exteriorizing procedure, of the Mikulicz type, should be employed. It must be stated, however, that this technic could not be used in over one-third of our cases. Resection should be avoided in the acute stage of the disease.

(9) It is impossible to differentiate between carcinoma and diverticulitis in a few cases. In these, resection is indicated.

(10) Resection of the involved segment of the bowel appears to offer patients suffering from the more severe and complicated forms of diverticulitis the greatest hope for improvement. If carefully planned, the mortality should be low, serious complications few, and unsatisfactory late results infrequent.

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DISCUSSION.—DR. HENRY W. CAVE (New York): The first cases of perforated diverticulitis with abscess formation in the American literature were reported by Dr. George Emerson Brewer, an attending surgeon at the Roosevelt Hospital, before the American Surgical Association, in May, 1907 (35 years ago). He reported six cases.

To some of us, certain suggestions offered by Doctor Smithwick in the surgical management of diverticulitis seem, at first, radical; and they are radical, when compared with our former notions of colon surgery. But, assuredly, he has shown that the morbidity and the mortality can be lowered in properly selected and properly prepared patients. No doubt, with the judicious use of the newer chemotherapeutic agents and methods of proximal decompression, the operative mortality can be still further reduced.

In the past, most of us have treated the complications of the disease, rather than attacking primarily the disease itself; this has necessitated emergency surgical measures. Whereas, Doctor Smithwick has not stopped at that, but has gone on with elective procedures which promise a more effective and lasting cure.

Cancer and diverticulitis are not infrequently seen coincidentally, but there is no evidence to assume that the presence of diverticulosis or diverticulitis predisposes to the development of a malignancy; this is accepted by all of us.

The statement is accredited to the late Dr. Daniel Jones, of Boston, that bleeding from the rectum is a prime symptom of malignancy and not diverticulitis. Doctor Smithwick has stated that a history of bleeding is present in 15.7 per cent of patients known to have diverticulitis. It is the experience of most of us that patients with the history of rectal bleeding, sent to the roentgenologist for a barium enema, return with a report of diverticulosis or diverticulitis and not cancer.

In eight, or 24.2 per cent, of the 33 cases resected by Doctor Smithwick, the history, the roentgenographic findings, and the operative findings, all suggested malignancy; and there was no other way except resection, to answer the problem; usually the involvement is beyond the reach of the sigmoidoscope and the tell-tale biopsy specimen.

From 1920 to 1942, a 21-year period, at the Roosevelt Hospital, 43 patients of a group of 116 admitted to the Surgical Service were operated upon for acute or chronic diverticulitis; of these, 11, or 25.6 per cent, were explored for a possible or probable malignancy. These figures on this particular point in the two series, the one from the M. G. H. the other from the Roosevelt Hospital, are almost identical.

In other respects, our series correspond similarly to those of Doctor Smithwick, as to the indications for surgery, the methods of approach, and the mortality; except that in no instance have we resected the sigmoid for recurrent attacks of diverticulitis *per se*.

Doctor Smithwick has resected the sigmoid in 33 individuals, with a relatively low mortality rate of 17.1 per cent, considering the nature of the disease. And, in a group of 12 of 33 resected, he had a surprisingly low mortality of 6.1 per cent.

To me, this group of 12, resected because of recurrent attacks of diverticulitis, is one of the principal features of his splendid presentation.

Preliminary proximal colostomy he considers preferable to cecostomy, and should be done in all cases where resection of the sigmoid is to be carried out. The wider the excision, the lower the chance of leakage at the suture line; and added security by suturing healthy bowel wall.

Wisely has he set a time interval of from three to six months of proximal decompression, by colostomy, before proceeding with the resection.

Stenosis as a complication at the site of removal is not infrequent by the Mikulicz method in our own series.

In dealing with an inflammatory and not a malignant lesion, I believe it can be stated with fairness that any type of exteriorization procedure is as complete and, to me, is safer, than suturing the colon end-to-end, or even side-to-side; and I say this even in spite of the sulfonamide drugs and the Devine method of dysfunctioning the left colon.

In the series here presented, colostomies were closed in 36 instances, and only 52.8 per cent remained well, indicating that the inflammatory lesion persisted. The late results following resection have proven more satisfactory.

Doctor Smithwick, I am sure, has stimulated us in an attempt to completely eradicate the diseased segment of the colon, thus permitting these individuals to be well and not semi-invalids.

DR. RICHARD B. CATTELL (Boston, Mass.): Doctor Smithwick's presentation of the difficulties of diverticulitis is of unique interest, since there are 64 patients treated by every possible method of treatment that could be applied to diverticulitis, and they are an unselected group. I think he has demonstrated, very conclusively, that a reasonable mortality can be expected if we delay resection to be a late and elective procedure.

Doctor Walker and I have recently reviewed our patients who have been operated upon for diverticulitis at the Lahey Clinic. We think there are only two operative indications: one, the complications of inflammation, and second, and most important, the indication of obstruction.

I would like to propose a relatively different conception with regard to the treatment of abscess in diverticulitis. From our experience and from that in the literature, where free pus is drained into the peritoneal cavity, the mortality has been high. I believe that if we delay operation in those cases with abscess until they either point in the left lower quadrant or by rectum, and if operation is indicated, do not operate in the field where the diverticulum is located but establish a colostomy of the transverse colon, we will reduce the mortality. Furthermore, these abscesses frequently drain spontaneously into the lumen of the bowel.

We have, because of our own mistakes and high mortality, made another rule, very clearly brought out by Doctor Smithwick, and that is that with diverticulitis we do not perform a primary resection at any time, if we know with what we are dealing. Where we have resected the diverticulitis as a primary procedure with a mistaken diagnosis of carcinoma, our mortality has been 50 per cent. With regard to procedure of colostomy in the transverse colon if a long spur is formed greater ease will be experienced in the subsequent extraperitoneal closure.

DR. CARL EGGERS (New York): I rise to discuss Doctor Smithwick's paper, largely to call attention to the importance of the subject of diverticulitis and the danger associated therewith. In my own personal experience, the condition has not been uncommon. I have seen 82 cases with acute diverticulitis of sufficient severity to warrant a surgical consultation. In 36, or 43.9 per cent, a condition developed which required surgical intervention. In other words, 36 patients were operated upon either for perforation or obstruction or mistaken diagnosis. Of those operated cases, 20, or 24.4 per cent, had perforation. Twenty-four per cent of the acute diverticulitis cases had perforation. Their operation was forced on the surgeon. That is what I want to call attention to. That was the group we had to handle surgically. Of that group, ten died, a mortality of 50 per cent.

The total mortality in the 34 cases operated upon was 23.5 per cent, which is restricted entirely to acute perforations. Among this group there were five patients with cancer, all of whom eventually succumbed to their disease.

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Of the late complications which follow this condition, one of the most annoying is the persistent fistulae. If the fistulae discharge only suppurative material, the patients do not mind so much, and some prefer to have the fistula drain itself rather than be subject to operation, but if there are feces draining, there is a different condition. During the last four or five years we have had four such cases. One preferred to drain and finally healed after about four years. Two were operated upon, and by complete excision of the fistulae and closing the sigmoid opening, it was possible to heal them. The fourth one has had several attempts at closure, but it was not permanent.

Another interesting complication is sigmoid-bladder fistulae. I think much depends on the extent of the involvement in that and/or the place of attachment. If the place of attachment is close, the closure should not present much difficulty, if one uses prompt cleansing of the bowel and bladder both, and interposes a layer of omentum between the two sutures after completion. But the important thing is the danger of perforation. If the perforation can be avoided in some of the patients who have repeated attacks of pain and obstruction, an operation of choice in those patients may be indicated, as Doctor Smithwick has stressed, and there one can prepare them adequately the way one does in carcinoma. One of the difficulties with resection, however, in these cases is the length of involvement of the bowel. That is one of the very important differential diagnostic points. Carcinoma usually involves a small segment; diverticulitis, a long segment, so long you have to operate in diseased tissue if you want to resect the whole area. That is one of the very serious difficulties. Also, resection does not guarantee that one will not have recurrence. I have had two patients who had resection done, who later had recurrences, and one of them is under observation now. It was resected ten years and he was pretty well. Now he has recurrent attacks of severe pain resembling obstruction, and roentgenograms show very extensive diverticulitis along the whole sigmoid region.

DR. CHARLES C. LUND (Boston, Mass.): In connection with Doctor Smithwick's paper and Doctor Cave's comments on it, both mention the occasional incidence of bleeding in diverticulitis. I want to call attention to the fact that that bleeding may be quite severe.

A few months ago a patient at the City Hospital, in Boston, came in with a history of a marked hemorrhage of fresh blood. He was in such shape that the interns transfused him as soon as possible after admission. During the time that the first transfusion was running into his veins, he called for the bed-pan, and a measured amount of 1,500 cc. of pure blood was evacuated. Transfusions were repeated. Many pints of blood were given. We got far enough ahead of the hemorrhage so that, on the second morning, it seemed reasonable to try a desperate operation. The situation that was found was a fistula that had burrowed from a diverticulum into the ileac fossa. I did not feel justified, with the scarred conditions found, to try to do anastomosis. I tied off the artery; the patient did very well for a few hours, and then died of hyperpyrexia, which possibly is accounted for by the period of pretty severe shock, or low blood pressure, that he was in before the operation. I do not know; I think that is a unique case.

Doctor Berring and I have studied it to some extent. We find no reference to such an instance in either surgical or pathological literature. If any of you have had any experience approximating that, I would appreciate it if you would speak to me about it.

I think Doctor Smithwick's paper was really very, very valuable. In our experience, which has not been studied at the City Hospital, I would say it is my personal impression that when our cases have done well they have been handled in the way in which Doctor Smithwick's cases have been handled. When they have not done well, they have been handled in the way the cases at the General that have not done well have been handled, as he has shown.

DR. R. H. SMITHWICK (closing): I think the discussion this afternoon in regard to diverticulitis is fairly representative of what you find in the literature, namely, that there is considerable difference of opinion about what should be done and when it should be done. Strangely enough, although there is a great deal of literature on certain aspects of this problem, there are surprisingly few reports of late results of any maneuver, whatsoever. Many people, of course, have been operated upon, but there are very few late results in the literature, for which reason it is difficult for one to make a decision as to what really should be done under various circumstances. My impression is that there is a real need for further reports of late results of various forms of treatment.

SURGICAL TREATMENT OF MALIGNANT LESIONS OF THE SIGMOID—WITH EXTENSION*

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THE OPERABILITY of malignant lesions of the sigmoid is limited by the presence of distant metastases or the extensive involvement of adjacent structures, removal of which would jeopardize life. The necessity for resecting areas of small bowel, uterus, tubes and ovaries with the sigmoid has been met successfully and is not regarded as being particularly dangerous. When, however, the tumor invades the urinary bladder—especially if the invasion is extensive or happens to be near the trigone—operation has been approached in a spirit of defeatism even though the lesion be otherwise operable. Accordingly, many cases of carcinoma of the sigmoid are denied radical operation because the operator fears that resection of part of the urinary bladder with the bowel is too hazardous.

Little mention is made of this extension and its treatment in the literature covering the subject. In a few instances authors either condemn the technical gymnastics required or state simply that if the bladder involvement is small, entrance into that organ should not be feared if it is necessary to complete a radical resection. Yet it seems surprising that with what is known of partial or complete cystectomy for other conditions we should not encounter more reports of experience with the partial removal of the urinary bladder in cases of carcinoma of the sigmoid with extension. The purpose of this communication is to compare the results in two cases of carcinoma of the sigmoid with involvement of the urinary bladder in which we accepted the idea of palliation solely because of the urinary bladder involvement with those in four others in which resection of the diseased portions of the bladder was carried out.

CASE REPORTS

Case 1.—N.Y.H. No. 274152: W. P., male, age 60, had complained of increasing constipation over a period of one year. Two months before admission the stools became narrow and abdominal cramps developed which were relieved by the passage of stools or flatus. There were no bloody stools. He had nocturia three to four times for the past two months, and had lost 60 pounds since the onset of his symptoms. The positive physical findings included evidence of weight loss, arteriosclerosis, complete edentia, and a palpable, fixed mass in the suprapubic region. Digital examination of the rectum was negative. Proctoscopic examination revealed a fungating lesion at 16 cm. that proved to be adenocarcinoma on microscopic examination. All laboratory tests were negative with the exception of occult blood found on stool examination. Exploratory celiotomy revealed a large tumor of the sigmoid invading the fundus and posterior wall of the bladder; no liver or distant lymph node metastases were noted. The lesion was considered inoperable, and a right transverse colostomy was performed. The patient is living, with little change in his condition, one year and two months following operation.

* Read before the American Surgical Association, Cleveland, Ohio, April 6-8, 1942.

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Discussion: Resection in this case would have required the removal of two-thirds of the bladder with the sigmoid by the abdominoperineal method. The radical operation should have been attempted.

Case 2.—N.Y.H. No. 282163: E. C., male, age 60, was admitted to the Urological Service, with the complaint of weight loss, watery diarrhea and later constipation for a period of one year. Six to seven months previously there developed tenesmus, urinary frequency and burning on urination. Two months before admission the patient observed the passage of gas from the urethra. These symptoms became progressively worse and weakness became pronounced. Examination revealed emaciation, a mass in the left lower quadrant and suprapubic region and an enlarged prostate. All laboratory examinations were negative except for the stools which were positive for blood. Pyelography revealed left hydronephrosis and left hydroureter. Cystoscopic examination revealed a large defect in the fundus of the bladder, due presumably to carcinoma of this organ. Barium enema showed an irregularity in the sigmoid, and on proctoscopic examination a lesion was seen at 15 cm. which proved to be adenocarcinoma. A transverse colostomy, without exploration, was performed under local anesthesia. Postoperatively, feces and gas continued to pass per urethra. Severe lower abdominal pain developed on the ninth post-

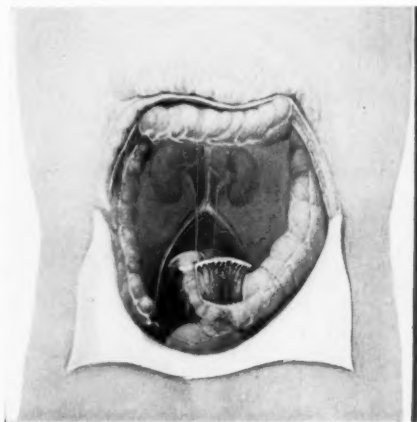


FIG. 1.—Case 3: Extension of carcinoma into the fundus of the bladder.

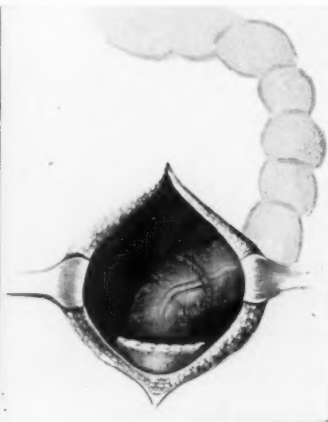


FIG. 2.—Case 3: Repair of bowel and bladder at end of operation.

operative day, with signs of peritonitis from which he died on the next day. Postmortem examination revealed carcinoma of the sigmoid infiltrating the fundus of the bladder, resulting in rectovesical fistula, extravascular abscess with perforation and generalized peritonitis.

Discussion: The transverse colostomy was established as a preliminary step to radical resection, and the postmortem findings confirmed the suspicion that the growth could have been removed if infection had not terminated the patient's life.

Disappointed by the poor results of such palliative procedures, we have been led to perform much more extensive operations in the following four cases including, when necessary, wide resection of the bladder.

Case 3.—N.Y.H. No. 199533: L. B., female, age 65, had noticed increasing constipation for three months, with ribbon stools for one month, and occasional abdominal cramps. No bloody stools were noted, and there was no weight loss. Physical examination showed moderate arteriosclerosis but was otherwise negative. Stools were negative for blood. Barium enema showed constriction of the sigmoid. Proctoscopy was negative.

Procedure: Exploration revealed that there was a large tumor of the sigmoid fixed to the fundus of the bladder but that actual invasion of the bladder was not extensive. A portion of the fundus was excised with the bowel tumor, thus freeing the intestinal mass. This was resected radically and end-to-end anastomosis performed. The resultant opening in the fundus of the bladder was sutured with catgut and silk, and a cecostomy was performed. The abdominal wound was closed with catgut and silver wire retention sutures and a retention catheter was inserted per urethra.

Course: The abdominal wound became infected but responded to simple drainage. The urinary catheter was removed on the eleventh postoperative day. Normal bowel movements occurred on the twenty-sixth day.

Follow-Up: There is no sign of recurrence three years and ten months postoperatively.

Case 4.—N.Y.H. No. 274729: A. B., male, age 66, had complained of passage of gas per urethra for a period of two months, urinary frequency, burning, and failure to empty the urinary bladder completely when voiding. Bowels were regular but the stools con-

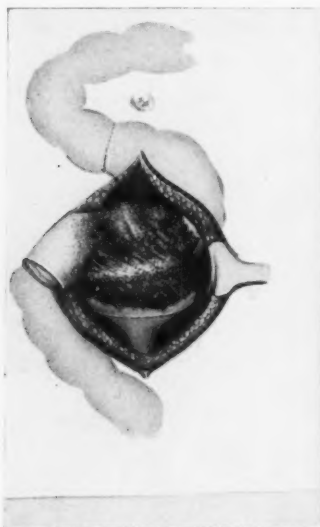


FIG. 3.—Case 4: Extensive involvement of upper half of urinary bladder.

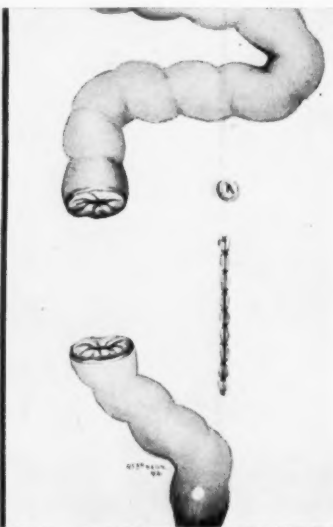


FIG. 4.—Case 4: Remaining bowel segments, later anastomosed end-to-end.

tained pink, jelly-like material at times. He had a poor appetite due to the fact that eating made all the symptoms worse, and had lost 25 pounds in weight.

Physical Examination showed obesity and moderate arteriosclerosis. There was a hard suprapubic mass, about the size of a grapefruit, which was slightly tender. The prostate was moderately enlarged. Laboratory tests showed 3+ albumin and numerous W. B. C. and R. B. C. in the urine. All stools were positive for blood. Proctoscopic examination was negative. Barium enema showed a lesion of the sigmoid resembling diverticulitis.

Preoperative Course: The patient was placed on clear liquid diet, with definite improvement. A second barium enema showed no change from the first. Soft diet was instituted at this time, with a return of the symptoms, and the passage of feces in the urine as well as more gas per urethra was now noticed.

Procedure: Because of his failure to improve, transverse colostomy was attempted under local anesthesia. A greatly redundant sigmoid, which was encountered in the wound, necessitated using the portion of that organ proximal to the lesion for the colostomy instead of the transverse colon. Following this, the patient improved con-

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siderably, the passage of gas and feces per urethra being markedly decreased. His course following the colostomy was complicated by a pulmonary embolus, but recovery was prompt. Thirty-eight days after the colostomy, under open drop-ether anesthesia, a left rectus incision was made, and the huge lesion in the sigmoid was found to involve the upper half of the urinary bladder. On first inspection, complete fixation of the mass with a considerable amount of infection was noted. However, there were no distant metastases, and an attempt was, therefore, made to free the mass. The peritoneum covering the bladder was incised together with the peritoneum lateral to the sigmoid. This allowed a line of cleavage which resulted in the mobilization of the bladder with the intestinal tumor. Further examination of the large mass revealed that if radical removal were to be carried out it would necessitate the excision of two-thirds of the bladder. At the proper site, just above the trigone, the bladder wall was incised, and by carrying the incision completely around the bladder the entire mass was mobilized enough to allow it to be raised outside the abdominal cavity. Kocher clamps were placed on the bowel at suitable distances below the lesion, and by dividing between the clamps the mass was further delivered, so that the mesentery beneath the tumor could be clamped and resected. After removing the proximal bowel to the level of the colostomy, the resection was completed.

At this point, however, the patient was in moderate shock and, although an anastomosis would have been possible, it was deemed wiser to leave the colostomy opening undisturbed and bring the distal segment out through the lower right rectus region. After securing proper hemostasis of the mesentery and bladder wall, the circular bladder edge was sutured around the end of a mushroom catheter, which was then brought out through the lower end of the left rectal wound as a cystostomy tube. Several cigarette drains were placed in the rectovesical pouch and the celiotomy wound closed with through-and-through silver wires. Shock was readily counteracted by the ordinary methods.

Pathologic Examination revealed adenocarcinoma of the sigmoid with extension into the urinary bladder, metastases to the regional lymph nodes, markedly inflamed and necrotic bladder wall, and a small polyp in the sigmoid.

Course: Unremarkable until the tenth postoperative day. The cystostomy tube was removed and several hours later there was an alarming hemorrhage from the suprapubic wound as well as from the urethra. This ceased after half an hour, and, with the aid of transfusions, the patient's condition improved. A retention urethral catheter was inserted on the twentieth postoperative day. The wound healed rapidly, and following removal of the catheter on the forty-fifth postoperative day, the patient was able to void satisfactorily. He was discharged 66 days after the radical procedure. At this time the left rectus wound was completely healed and the right rectus region contained two colostomy openings—the upper one, being proximal, was the functioning colostomy.

Improvement was now quite rapid. The patient returned to work, but was considerably handicapped by the nuisance of the colostomy. Six months after the resection he was readmitted to the hospital, and after four days of preparation with sulfadiazine, irrigations and clear liquid diet, under open drop-ether anesthesia, the two colostomy openings were dissected free of the abdominal wall, the ends of both resected about two inches from the opening, and end-to-end anastomosis performed, without proximal decompression. Sulfadiazine was continued postoperatively, to include seven days in all. Passage of flatus was noted in 72 hours, the bowels moved normally on the fifth day, both wounds healed per primam, and he was discharged on the twentieth postoperative day.

Follow-Up: The patient now weighs 220 pounds, and has normal functioning bowel and bladder behavior. There is a small incisional hernia in the left rectus wound. There is no sign of recurrence or metastases one and a half years following the resection.

Case 5.—N.Y.H. No. 297121: S. Z., male, age 51, complained of diarrhea, urgency, tenesmus and passage of foul-smelling mucoid material per rectum. A slight amount of blood was passed with the stools. There were intermittent abdominal cramps, urinary

frequency, cloudy urine, and the passage of flatus per urethra at times. There had been a loss of weight of 64 pounds.

Physical Examination showed emaciation, and a palpable, large, hard, fixed mass in the rectovesical pouch. Proctoscopy revealed a fungating mass at the level of 15 cm., proven to be adenocarcinoma microscopically. Laboratory tests showed 2+ albumin, and many W. B. C. and R. B. C. in the urine. R. B. C. 2.5 million; W. B. C. 21,000; stools positive for blood. Cystoscopy showed intrusion and invasion of the bladder wall by bowel malignancy.

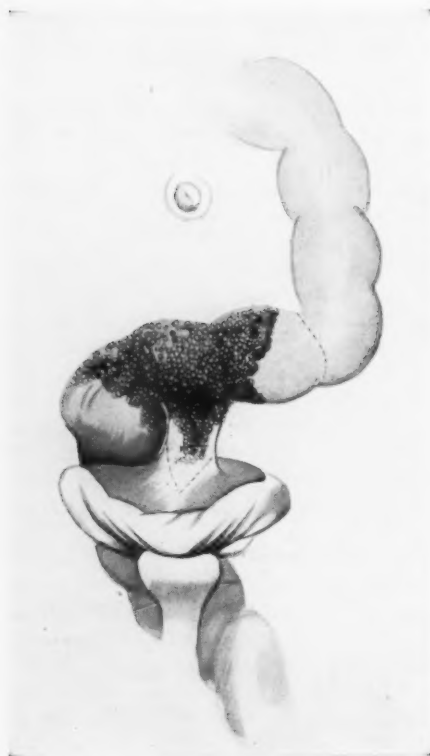


FIG. 5.—Case 5: Extension of carcinoma into posterior aspect of the bladder.

wall, and, after locating the right ureter which was obstructed by the tumor, the posterior peritoneum was incised and the mass finally freed sufficiently to be delivered into the wound. The section with the invaded bladder wall attached was now resected with adequate margin in the bowel and mesenteric areas. Because the lesion was situated low, it was impossible to make an anastomosis. The lower end of the bowel was, therefore, turned in and the proximal end was brought out the upper region of the wound. A tube was inserted in the fundus of the bladder and brought out the lower end of the wound. Several cigarette drains were placed in the rectovesical pouch, and the wound closed with through-and-through silver wire sutures.

Course: Sulfadiazine was continued for a period of seven days. The suprapubic tube was removed on the tenth postoperative day, and on the twenty-fourth day the patient was voiding normally. His condition improved markedly, and there was immediate cessation of the urinary inflammatory symptoms. He was discharged 41 days after the resection, with the wound completely healed. The transverse colostomy is the functioning anus, and there is a mucous fistula present in the left rectus incision.

Procedure: Transverse colostomy was performed under local anesthesia. After opening the colostomy the patient improved slightly, but began to run a septic course with high temperature and chills, due to marked urinary infection. This continued with a consequent downhill course until his condition became precarious. Several observers felt that because of the urinary infection, fixation of the mass, and obvious bladder invasion, resection would not only be dangerous but futile. However, after many transfusions and prophylactic administration of sulfadiazine, a midline incision was made under ether anesthesia. There were no metastases in the liver and no preaortic lymph nodes were involved. A greatly inflamed mass was located in the sigmoid, which was fixed to the posterior bladder wall. After incising the bladder peritoneum, the entire mass, with the bladder, was freed. The bladder involvement extended almost down to the trigone in a longitudinal manner. Incisions were made into the bladder, allowing margins on both sides. When the tumor was removed from the bladder there remained a long longitudinal incision in the posterior wall from the fundus to the region of the trigone.

After securing hemostasis, this was closed with interrupted catgut sutures. The tumor was still fixed to the posterior peritoneal

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Follow-Up: Ten months postoperatively there is no recurrence and no evidence of metastases. He has gained weight and strength and is voiding normally.

Case 6.—N.Y.H. No. 284479: J. J., male, age 51, had noted malaise, chills, fever, and a dull pain over his lower abdomen for three weeks. There was marked urinary frequency, dysuria and cloudy urine. Constipation became more marked during the past two months. He had passed a single bloody stool one month before admission.

Physical Examination showed a pale, acutely ill man. Abdominal and rectal examinations were negative. Laboratory tests showed many W.B.C. and R.B.C. in the urine; R.B.C. 3.3 million; W.B.C. 32,000; stools negative for blood. Proctoscopy revealed no tumor, but what appeared to be urine could be seen dripping into the rectum. Cystoscopy showed a rectovesical fistula located just above the trigone. Barium enema revealed a lesion of the sigmoid suggestive of carcinoma.



FIG. 6.—Case 6: Extensive involvement of posterior bladder wall.



FIG. 7.—Case 6: Marked involvement of bladder present six months after first resection.

Procedure: A transverse colostomy was performed, which resulted in marked improvement in his general condition. Many blood transfusions were given and sulfadiazine was administered preparatory to resection, which was attempted through a left rectus incision, three weeks following the colostomy. No liver or distant lymph node metastases were noted. The tumor was located in the sigmoid, and extension was discovered into the bladder in one small area in the region of the trigone. There was a considerable amount of infection present. An incision was made into the bladder "coring-out" the fistulous tract, but this could not be accomplished with a large margin because the ureteral orifices were in close proximity to the invaded area, but because of so much infection it was hoped that the actual invasion would be minimal. The opening in the bladder was closed with catgut. It was now fairly simple to free the sigmoid, resect it with good margin, and perform an end-to-end anastomosis. Two cigarette drains were placed in the rectovesical pouch and the wound closed with catgut and silver wire retention sutures. A retention catheter was placed in the bladder per urethra.

Course: An intra-abdominal abscess developed, which was drained three weeks postoperatively. Following this, improvement was marked and healing of the wound was rapid. Six weeks after the resection the transverse colostomy was closed, and the patient was discharged, with normal rectal and bladder function. He gained in weight and strength and remained well until six months following the resection. At this time he began to have hematuria, which was severe and continuous. Profound anemia and weakness followed. Cystoscopic examination at the time revealed the entire urinary bladder to be involved in an infected neoplastic process, biopsy of which proved it to be

adenocarcinoma originating from the rectum and showed the same morphologic structure as that seen in the sigmoid lesion. Roentgenotherapy offered no hope and nothing was planned therapeutically until the patient and his family insisted that anything be attempted which might offer even the slightest hope. Accordingly, bilateral ureterostomies were performed, following which the patient's condition improved rapidly. After several blood transfusions and sulfadiazine prophylactically, the left rectus wound was reopened and, again, no liver or distant lymph node metastases were noticed. There were a few small involved nodes in the mesentery beneath the anastomosis. The urinary bladder was enlarged and was obviously involved with tumor in its entirety. The bladder peritoneum was incised and the entire bladder freed by blunt dissection, continuing this dissection anteriorly under the symphysis and posteriorly so that both seminal vesicles and prostate gland were now clearly defined and freed. The posterior urethra was incised and vessels clamped, following which the bladder, prostate and seminal vesicles were removed *en bloc*. The sigmoid was again resected, leaving a small stump of rectum in the rectovesical pouch which was turned in by silk sutures. The proximal loop was brought out the upper end of the left rectus wound and cigarette drains were placed in the rectovesical pouch. The lower portions of the ureters were, of course, removed with the bladder. The patient withstood this procedure well. Some difficulty was encountered with the ureterostomies, but the patient improved to such an extent that he was up and about the ward. After several months of improvement, his condition began to decline and he died with palpable carcinoma in the rectal stump and obvious metastases in the liver, 13 months after the first resection, and six months after the radical resection of the bladder, prostate, seminal vesicles, ureters and sigmoid.

Discussion: Because of the site of invasion which was in close proximity to the interureteral ridge, the bladder involvement was not given a proper margin in the first operation. The second radical resection was, in reality, experimental, but might have offered the patient a slight chance of recovery. It is obvious from the course that had the second radical procedure been carried out originally, a better result may have been anticipated.

SUMMARY

It should be pointed out that a redundant sigmoid colon is one which attaches itself to the bladder and, therefore, allows extension of its tumors into the bladder. If no redundancy is present, the sigmoid usually lies against the posterior abdominal and pelvic walls, which position reduces the possibility of extension. The redundancy, however, is an asset if resection is to be performed.

The use of preliminary colostomy and prophylactic sulfonamide therapy, as well as the other better known preoperative agents, is recognized in the preparation of these patients for operation.

These cases are presented as evidence supporting radical operations in malignant disease of the sigmoid with extension into the urinary bladder. It is suggested that neoplastic involvement of the bladder is no reason, in itself, to withhold the radical operation. Partial resection of the urinary bladder may be accomplished without significant danger to the patient or resultant malfunction of the genito-urinary system. The operation of total cystectomy, seminal vesiculectomy and prostatectomy, combined with resection of the sigmoid neoplasm *en bloc*—if that is necessary to offer cure—is demonstrated to be possible.

Whether or not the patient with bilateral ureterostomies and permanent

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colostomy is one whose life in such a state is a fair exchange for death from carcinoma of these organs cannot be decided with accuracy until many similar cases and their experiences are recorded.

DISCUSSION.—DR. VERNON C. DAVID (Chicago): Doctor Bowers has brought to our attention a very important viewpoint in the treatment of malignant lesions of the large bowel, in that he advocates in this radioresistant group of tumors an extension of the indications for radical removal. The principles underlying this extension of indications for radical surgery must include a reasonable mortality rate and long-term survival rate as well as reasonable assurance that the growth and its extensions are completely removed.

I have been asked to discuss this paper because Doctor Gilchrist and I have recently reviewed our experience, during a ten-year period, of 179 radical operations for cancer of the rectum, where there were 74 favorable cases, with no question of operability, and another group of 105 patients having one or more doubtful factors which clouded operability (Table I).

TABLE I

CAUSES OF QUESTIONABLE OPERABILITY IN 105 PATIENTS

Over 65 years of age.....	38
One or two nodules in the liver.....	15
Adiposity.....	10
Obliterative pelvic peritonitis.....	9
Resection of prostate or urethra with the rectum...	7
Resection of rectovaginal septum with the rectum...	6
Peritoneal plaques over the tumor.....	5
Diabetes.....	5
Removal of all or part of uterus or adnexa.....	4
Adherent to prostate (removal of capsule).....	4
Adherent to bladder.....	4
Adherent to rectovaginal septum.....	6
Adherent to sacrum.....	4
Adherent to uterus.....	1
Resection of another loop of bowel.....	1
Marked coronary disease.....	2
Pregnancy.....	2
Removal of local recurrence.....	3
Fixed to abdominal wall.....	2
Asthma and bronchiectasis.....	1
Involvement of inguinal nodes.....	2
Double carcinoma of the rectum.....	1
Involvement of rectal fistula by adenocarcinoma of the rectum.....	1

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In the favorable group the hospital mortality was 4.3 per cent, and in the doubtful factor group it was 9.5 per cent.

In the group where the indications for operation were liberal, there were 38 patients over 65 years of age, with a mortality of four, or 10.5 per cent (Table II).

TABLE II

AGE AND RADICAL OPERATION FOR CANCER OF THE RECTUM

18 patients between 65-70 years....	1 death—embolism
12 patients between 70-75 years....	1 death—embolism
4 patients between 75-80 years....	1 death—pneumonia
4 patients between 80-85 years....	1 death—pneumonia
38 patients over 65 years.....	4 deaths—10.6%

Where the tumor was adherent to structures outside of the bowel we resected part of the prostate in 11, the rectovaginal septum in six, the dome or posterior half of the bladder in one, a part of the base of the bladder in five, the uterus or adnexa in five, the ureter in two, the urethra in one, and another loop of bowel in one. In this group of patients there were three postoperative deaths. In four other patients with carcinoma

of the sigmoid we resected the dome or posterior half of the bladder, with one death. Time does not permit details of long-term survival but I can say that while there will be a higher percentage of local recurrence in this group than in a favorable group, there will also be many patients who live three to five years after the operation.

We have not been impressed with the soundness of undertaking radical operations where definite liver involvement is present. However, there are patients having one or two doubtful nodules in the liver at the time of operation where the differential diagnosis between cancer and adenoma or lymphangioma of the liver is difficult to make. We believe it proper to carry out the radical operation in such patients. Of 16 such instances, four have died of cancer of the liver on an average of ten months following operation; four are alive three to five years postoperatively.

Adiposity, obliterative peritonitis, lymph node enlargement, circumscribed perforation of the tumor or fixation to the abdominal wall have not been considered as contra-indications to radical removal of the tumor. In carcinoma of the sigmoid, descending colon and cecum, with fixation to the abdominal wall, wide removal of the abdominal wall with the tumor has resulted in several five-year cures.

Until surgery is supplanted by a better method of treatment in cancer of the bowel, we believe that the indications for radical surgery should be broadened, for even though the mortality rate will be higher and recurrences more frequent, a larger number of patients will be given the chance of a long-term cure.

DR. RICHARD K. GILCHRIST (Chicago): On examining specimens of carcinoma of the sigmoid which required resection of viscera firmly adherent to them, we have been surprised to see how often this fixation is due to inflammation and not to extension of the tumor.

This slide shows the resected specimen of carcinoma of the sigmoid with resection of a full-thickness of the bladder. The large marker leads into an abscess cavity between sigmoid and bladder; the three smaller markers serve to identify diverticula above the tumor.

The second slide shows this same specimen from the other side. Sections through the wall of the bladder fail to show carcinomatous invasion; the fixation was by inflammation. It is interesting to note that the three diverticula are in line with the point of fixation around the abscess.

This second patient had a large carcinoma and the resected specimen of the sigmoid and full-thickness of the bladder is shown. There are three fistulae into the bladder; each of these showed carcinomatous infiltration.

Of five specimens where the full-thickness of the bladder was resected with the carcinoma of the sigmoid, one had carcinomatous infiltration, in three the fixation was by firm inflammatory adhesions, and one specimen was lost and the original sections were not taken through the adherent area. Interestingly enough, among nine other specimens of carcinoma of the sigmoid firmly adherent to other loops of bowel, uterus or abdominal wall, the fixation was due to inflammation in seven and infiltration in two.

It seems to me that we are apt to lose sight of the fact that the sigmoid may have become firmly adherent to the bladder or other viscera as a result of previous diverticulitis. Carcinoma is then superimposed upon this. With obstruction and the accompanying inflammation, it is impossible to tell the extent of the carcinoma. Of course, the inflammatory fixation may be due to slight perforation of the tumor and infection about this. These findings have led us to the conclusion that in carcinoma of the sigmoid the local mass outside of the bowel is very apt to be due to inflammation. This inflammation either arises from diverticula or results from inflammatory perforation of large, obstructing tumors. Many of these can be successfully resected with a fair chance of permanent cure. One precaution must be taken. When the tumor is firmly adherent to another structure there is often an abscess between the two. Therefore, we do not separate firmly adherent structures but attempt to resect a sufficient layer of the structure adherent to the sigmoid so that the abscess is not opened.

DR. RICHARD B. CATTELL (Boston): Doctor Bowers has taken a step that I think is very laudable, in extending operative indications to a very marked extent. Doctor Sugarmaker and I have just reported this month on our cases from 1939 through 1941. Eighty-six per cent of all patients during that period with carcinoma of the bowel had

CARCINOMA OF SIGMOID

a resection. Twenty per cent of all of those cases had invasion of some organ, either bladder, small intestine, or other organs. Ten per cent of them had liver metastases, and during this period we have resected the secondary metastasis in the liver in three cases. I think that until we have tried extensive resection in malignancy much more than we have at present, we should continue with such efforts as Doctor Bowers has made.

DR. RALPH F. BOWERS (closing): I want to thank Doctor David and Doctor Cattell for expressing an opinion about these radical procedures.

Doctor Gilchrist made a point that I believe got us into trouble in the last case. It is almost impossible, with the extensive infection that is present, to tell which is infection and which is tumor. Our experience with the first three cases has shown that the invasion of the bladder was not as marked as we thought. But we were able, by reason of that fear, to give the involved portion of the bladder a very good margin. In the last case, because extension was in the region of the trigon, we believed that infection would be present to a greater extent than tumor; therefore, the coring-out, and, subsequently, the recurrence.

I did not make the point clear, but I think that in the last case, had we undertaken the radical procedure, with the first part of the operation, we might have offered now a permanent cure.



LONG REMEMBER

In the Civil War nothing was known of "germs." Bacteriology was an unknown science.

"It can be understood," wrote Dr. William W. Keen, "why we surgeons in 1861-65, utterly unaware of bacteria and their dangers, in our ignorant innocence committed grievous mistakes which nearly always imperilled life and often actually caused death. May *le bon Dieu* forgive us our sins of ignorance. We operated in our old blood-stained and often pus-stained coats, the veterans of a hundred fights. We operated with clean hands in a social sense, but they were undisinfected hands. To the surgeon the spotless hands of a bride are dirty. We used undisinfected instruments from undisinfected plush cases, and still worse, used marine sponges which had been used in prior pus cases and had been only washed in tap water. If a sponge or an instrument fell on the floor it was washed and squeezed in a basin of tap water and used as if it were clean.

"Our silk to tie blood vessels was undisinfected. One end was left long hanging out of the wound and after three or four days was daily pulled upon to see if the loop on the blood vessel had rotted loose. When it came away, if a blood clot had formed and closed the blood vessel, well and good; if no such clot had formed then a dangerous 'secondary' hemorrhage followed and not seldom was fatal. The silk with which we sewed up all our wounds was undisinfected. If there was any difficulty in threading the needle we moistened it with (as we now know) bacteria-laden saliva, and rolled it between bacteria-infected fingers. We dressed the wounds with clean but undisinfected sheets, shirts, tablecloths, or other old, soft linen rescued from the family rag bag. We had no sterilized gauze dressings, no gauze sponges."

—Ciba Symposia.

THE MECHANISM OF ACTION OF ROENTGENOTHERAPY UPON INFECTION*

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AMONG both surgeons and roentgenotherapists there is much difference of opinion regarding the value of roentgen ray irradiation in the treatment of acute infections. This may be attributable, at least in part, to the fact that it is difficult and often impossible to evaluate, by clinical means alone, the merit of a therapeutic agent which has an effect short of a specific one. Such an evaluation is possible only by means of controlled comparative studies in volume, circumstances attainable only in animal experiments. A report of an investigation of this kind follows.

Experiments.—The original problem was designed to determine the effect of the sulfonamide drugs as well as roentgen ray irradiation upon peritonitis. But, as the investigation progressed, certain unanticipated findings appeared and altered the direction of study. Since the intraperitoneal route of bacterial inoculation was used in the original experiments it was continued throughout, to provide a consistent basis for comparison. For the inoculations a pathogenic culture of hemolytic *E. coli* was used. This culture was obtained from the Agricultural College, where it had been isolated from calves afflicted with a severe epidemic type of dysentery. Its minimal lethal dose for rabbits was established at two slants of 48-hour growth.

The micro-organisms from the slants were injected into the peritoneal cavity suspended in a standard solution of gastric mucin. In each series of experiments several animals were inoculated at the same time and, to be more certain that each animal received an equal number of micro-organisms, the slants were pooled, and from the pool each animal received 20 cc. of the mucin suspension, which in each instance provided the minimal lethal dose of bacteria. One and usually two or more recipients of each pool were reserved as control animals to verify, constantly, the virulence of the culture. On three occasions a control survived, and in each series represented by these controls all observations were discarded as invalid and the investigation halted until the original virulence of the culture had been restored by passage through animals.

The only criterion by which the effectiveness of the therapeutic agent was judged was survival and, to a lesser extent, the duration of survival. No records of temperature or other physical evidence of infection and toxemia were obtained.

* Read before the American Surgical Association, Cleveland, Ohio, April 6-8, 1942.

ROENTGENOTHERAPY AND INFECTION

In several animals the evolution of the peritoneal exudate was followed. At frequent intervals after inoculation, exudate was aspirated and the bacteria and leukocytes in ten representative fields were counted and an average value calculated. But as it became apparent that these studies made no contribution to the problem at hand they were discontinued as a routine procedure. For the same reason this data is omitted from this report except for the two illustrative records (Table I).

TABLE I

REPRESENTATIVE PERITONEAL EXUDATES OF RABBITS AFTER INTRAPERITONEAL INOCULATION WITH A CULTURE OF HEMOLYTIC *E. coli* IN 20 CC. OF GASTRIC MUCIN

Rabbit No.*	Inoculated:		Progress	Bacteria	Polys.	Phagocytes	Monos.
	Time of Smear						
10.....	4-4-40, 3 P.M.			1 slant, about 36,000 M.			
	4-4-40, 6 P.M.		Very ill	Packed	55	Occasional	2
	4-5-40, 7 A.M.		Very ill	Approx. 100	80	2	1
	4-5-40, 2 P.M.		Improved	82	78	10	3
	4-6-40, 2 A.M.		Much improved	Scattered in clumps	48	7	5
	4-8-40, 5 P.M.		Well	Occasional	10	8	8
14.....	4-4-40, 3 P.M.			2 slants, about 72,000 M.			
	4-4-40, 6 P.M.		Very ill	Packed	21	0	4
	4-4-40, 8 P.M.		Moribund	Packed	12	3	1
	4-4-40, 10 P.M.		Dead				

* Both rabbits are from series used to establish a constant minimal lethal dose. Rabbit No. 10 received a sublethal dose.

Postmortem examinations were made on all animals, but since there was no consistent or significant difference in the findings within the peritoneal cavity individual reports are omitted. In no instance was there a picture of peritonitis as observed in man. There was always an increased amount of peritoneal fluid varying from 5 to 30 cc. It was slightly to moderately turbid and usually blood-tinged but never thick and grossly purulent. The peritoneal surfaces were only slightly to moderately injected but, in common with the omentum, usually contained a few to numerous punctate areas of hemorrhage. There was definitely more injection of the peritoneal surfaces of the irradiated animals. The bowel was distended. Fibrin was singularly absent. The pleural cavities usually contained a small amount of clear fluid.

In five animals blood cultures were taken immediately following inoculation and every 15 minutes for one hour. All cultures were sterile.

In establishing the minimal lethal dose of the culture it was found that the quantity necessary consistently to cause death did so within 12 hours. Some of the animals which survived longer than 12 hours when a lesser dose was given, recovered. Therefore, the larger or consistently fatal doses were used throughout the experiments.

The Effect of Sulfanilamide and Sulfathiazole.—In eight rabbits the abdomen was opened under local infiltration anesthesia. In each of six, one Gm. of sulfanilamide powder was spread widely over the peritoneal cavity, and in two of these the abdomen was simply closed. In the remaining four, the

wounds were closed around small catheters through which the peritoneum was inoculated and then the catheters removed. This procedure assured retention of all the injected fluid. Two animals served as controls and received only inoculations given through catheters.

The two controls died in six and 11 hours; the four sulfanilamidized and inoculated rabbits died in four, five, eight and ten hours. The two which received only sulfanilamide survived and despite the fact that they received enormous doses, at no time did they show evidence of drug intoxication.

An identical series of studies with sulfathiazole gave essentially the same results, except that one of the two rabbits which received only sulfathiazole died on the third day, with postmortem findings of patchy consolidation of both lungs.

In a third series, seven rabbits were given the culture intraperitoneally. Two served as controls and died in five and one-half and seven hours. One hour before inoculation each of the remaining five were given 50 cc. of 0.8 per cent solution of sulfanilamide subcutaneously. They died four, five, five, six, and eight hours after inoculation.

In a fourth series, four rabbits were given the culture and 1 Gm. of sulfanilamide intraperitoneally and one, a control, was given the culture only. This series differed from the others in that the peritoneal cavity was not opened. The sulfanilamide powder along with the bacteria was suspended in the solution of mucin and deposited in the peritoneal cavity through a needle. All animals died. The periods of survival were five, ten, 14, and 14 hours. The control lived ten hours.

Not only did the use of sulfanilamide and sulfathiazole powder, as topical applications, and as subcutaneous injections, fail to prevent death of these animals, but it actually decreased the duration of survival.

Roentgenotherapy.—All animals received irradiation according to a fixed formula. It was given through one anterior port over the entire abdomen, with the remainder of the body shielded with lead. It was delivered through an inherent filter of 3 Mm. aluminum and an added filter of 0.5 Mm. copper and 1 Mm. aluminum at 50 cm. target skin distance; activated by 140 kilovolt constant potential, and 15 milliamperes. The intensity of the beam was 20 r. per minute, measured in air. The dosage was determined by the duration of exposure and was varied accordingly.

Postinoculation Irradiation.—Ten rabbits were inoculated with two slants in 20 cc. of mucin. Two served as controls, and eight received roentgen ray irradiation immediately after inoculation. Of these two received a single dose of 100 r., and two, a single dose of 200 r. within 20 minutes after inoculation. They survived only five hours.

Four received 20 r. every two hours until they died five, six, six, and seven hours after inoculation. Both controls died in five hours. A possible cause of failure of roentgen ray irradiation to alter the course of events resulting from the inoculation in this series of animals is suggested in the results of the subsequent experiments.

Preinoculation Irradiation.—The rabbits in this series received roentgen ray irradiation at periods prior to inoculation varying from 16 weeks to 24 hours. In all, there were eight different intervals of time between irradiation and inoculation, and because the experimental procedure was not constant this series is reported under eight headings:

PERCENTAGE OF SURVIVORS AFTER INOCULATION AND X-RAY THERAPY

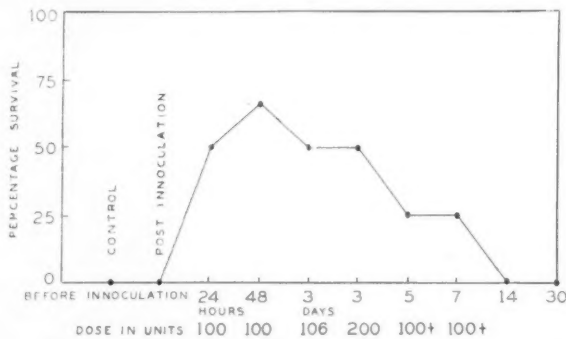
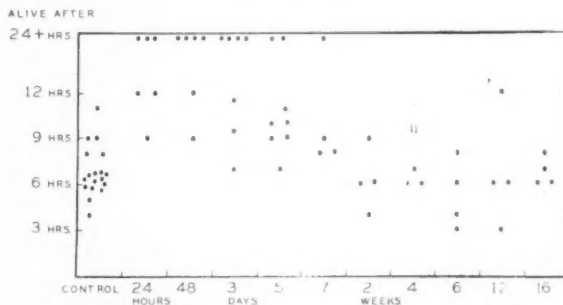


CHART 1.—When irradiation was given after inoculation there were no survivors, but when given 24 hours prior to inoculation, one-half of the animals survived. Protection reached a peak in 48 hours and then was rapidly dissipated.

DURATION OF SURVIVAL AFTER INOCULATION AND X-RAY THERAPY



PERIOD BETWEEN X-RAY AND INOCULATION

CHART 2.—From this scattergram it is apparent that the majority of the animals in the groups which received irradiation from 24 hours to five days before inoculation, and died, survived longer than those of the other groups.

Group I.—There were six rabbits in this group. Two received a single dose of 100 r, two a total dose of 300 r. in three daily doses, and two received a total dose of 600 r., administered in six daily doses. The latter two animals developed diarrhea, from which one died.

Sixteen weeks after the last roentgen ray treatment these animals were inoculated, and four died within eight hours while one survived. Two controls died in six and one-half and eight hours.

Groups II, III, IV and V.—These groups differ from the preceding one, only in respect to the intervals of 12, eight, six, and four weeks, respectively, which elapsed between the time of irradiation and inoculation. Eight of the original 24 animals which were irradiated died during the waiting period. The remaining 16 died within 11 hours after inoculation. The three controls died in four, six, and eight hours.

Group VI.—There were four rabbits in this group; two received 100 r., and two, 200 r. of roentgen ray irradiation in single doses. They were inoculated seven days later, and one of the two, which received 100 r., or 25 per cent of the group, survived. The others died in eight, eight, and nine hours.

Group VII.—There were eleven rabbits in this group. Four received 100 r., and four, 200 r. of roentgen ray irradiation in single doses, while three were used as controls. Five days later all were inoculated, and two, or 25 per cent of the irradiated animals, survived. The others died in seven, nine, nine, ten, ten, and 11 hours, and the controls died in five, nine, and nine hours.

Group VIII.—Eight rabbits were inoculated three days after receiving roentgen ray irradiation (four, 100 r., and four, 200 r.). Four (two, two), or 50 per cent, survived. The others died in six and one-half, nine, 11, and 11 hours. Three additional rabbits which served as controls died in five, six, and six hours.

Group IX.—Six rabbits were inoculated 48 hours after receiving 100 r. of roentgen ray irradiation. Four, or 66.6 per cent, survived and two died in nine and 12 hours. There were three controls, and these died in four, six, and 11 hours.

Group X.—Out of six rabbits inoculated 24 hours after receiving 100 r. of roentgen ray irradiation there were three, or 50 per cent, survivors. The three fatalities occurred in nine, 12, and 12 hours. The three controls survived only six, seven, and seven hours.

From this series of studies it is apparent that roentgen ray irradiation provided these animals with a considerable degree of protection against the inoculation of the lethal agent. This protective factor conveyed by irradiation was apparent within 24 hours, attained a peak of effectiveness on the second and third days, and then rapidly diminished. The number of animals used in these studies is much too small to provide statistical deductions. The figures have been reduced to percentages merely for purposes of visualizing apparent trends.

Killed Cultures.—Because all of the animals became prostrated within two or three hours after inoculation and because those that failed to survive died within 12 hours, and many within the brief period of four hours, an interest in the cause of death was aroused. It seemed unlikely that an infection could establish itself and develop to lethal proportions in such a brief period of time. It seemed probable that there was inherent in the culture, at the time of inoculation, a lethal dose of toxin. To determine the validity of this hypothesis the following studies were carried out with the

same culture, killed by heating in a water bath of boiling water for 12 minutes. The death of the culture was verified by failure of growth on culture media.

Eight rabbits were given intraperitoneal inoculations of two slants of the killed culture in 20 cc. of saline. Seven died and one completely recovered. One survived three days, and the others died in seven, eight, eight, nine, 12, and 18 hours.

From this data it seems reasonable to conclude that in the previous experiments with the live culture the animals died not from established peritonitis or from infection *per se* but rather from toxemia; that is an intoxication from the toxic factor which was present in lethal quantity at the time of inoculation.

At this point in the investigation and upon the suggestion of Dr. Alfred Brown, determinations of the hematocrit and quantitative measurements of serum protein were made upon five rabbits before, and five hours after, intraperitoneal inoculation of the killed culture. The first specimens were taken when the animals were in normal health and the second ones when they were prostrated. Because these studies showed the development of the blood changes characteristic of shock, hemoconcentration and hypoproteinemia, with the development of prostration, it seems fair to assume that the state of toxemia produced by both the live and killed cultures was essentially a state of shock. The results of these blood studies are detailed in Table II:

	Serum Protein		M.M. Packed Red Cells	
	Normal	Inoculated	Normal	Inoculated
1.....	5.98	4.78	30	34
2.....	6.47	4.92	31	38
3.....	5.85	4.62	25	36
4.....	6.22	5.15	27	36
5.....	6.15	5.02	30	37
Av.....	6.13	4.9	28.6	36.2

Obviously, the next problem to be investigated was the effect of prophylactic roentgen ray irradiation upon animals inoculated with the killed culture. Five rabbits were given 100 r. each of roentgen ray irradiation, and 48 hours later were inoculated with two slants of the killed culture. Three, or 60 per cent, of the series survived, and two died in 12 and 16 hours. Two additional animals which served as controls died in eight and 12 hours.

With this evidence that prophylactic roentgenotherapy is capable of reducing mortality from the killed culture, there arose the question of the mechanism involved. Is it a local effect resulting from the action of the rays upon the peritoneum or is it a general one?

It had been observed that 48 hours after irradiation the peritoneal cavity contained an increased amount of fluid, and that this fluid was very slightly blood-tinged. Microscopic studies had revealed the presence of

numerous red blood cells but only an occasional white blood cell and plasma cell. It seemed probable, however, that this fluid might contain some element which neutralized the toxin contained in the killed culture. Consequently, four rabbits were given 100 r. of roentgen ray irradiation, and 48 hours later were killed. The peritoneal cavity in each instance was opened and washed with 20 cc. of saline, which, as it was recovered by aspiration, carried along with it a maximal quantity of the peritoneal fluid. This fluid from each of the four animals was pooled and then mixed with eight slants of the killed culture, and after standing for 30 minutes at room temperature was injected into the peritoneal cavities of four stock rabbits. All, or 100 per cent survived. Two controls, run simultaneously, died within 12 hours.

To determine that this protective property resulted from roentgenotherapy and was not a normal constituent of peritoneal fluid, peritoneal washings from four untreated (stock) animals were obtained, pooled, mixed with eight slants of the killed culture and, after 30 minutes, injected into the peritoneal cavities of four stock rabbits. Three of them died in seven, nine, and 12 hours and one survived. Because this survivor never appeared ill it is possible that the fluid was injected into the lumen of the bowel.

Upon the assumption that the protective factor present in the peritoneal fluid following irradiation might also be present in the blood stream, four rabbits were given 100 r., and 48 hours later were exsanguinated by cardio-hemacentesis. The blood thus obtained yielded 84 cc. of serum, which was mixed with eight slants of the killed culture and, after remaining for 30 minutes at room temperature, was injected in equal quantities intraperitoneally in four stock rabbits. Three, or 75 per cent, survived, and one died after four days. Two controls died in ten and 14 hours.

The influence of serum from irradiated animals upon the live culture was tested in two rabbits. The procedure differed from that used in the preceding experiment only in that the live culture was used. Both animals survived. A single control died in ten hours.

As in the case of the peritoneal fluid there was the question of the presence of a protective factor in the serum of the normal untreated rabbit. Consequently, the serum from four such animals was mixed with eight slants of the killed culture and, after 30 minutes, was injected into four stock animals. Three died in eight, 14, and 17 hours, and one survived.

The excellent survival record in this last group of experiments may be attributed to the probable fact that the toxicity of the killed culture was much reduced before it was injected, as a result of its contact with the serum or peritoneal fluid for 30 minutes preceding injection. That this serum from irradiated animals contained an antitoxic factor seems a justifiable conclusion and, quite naturally, led to speculation relative to the possibility of using it for passive immunization. The question: Does this serum retain its effectiveness when given subcutaneously or intravenously either previous to, or simultaneously with, inoculation?

Five rabbits were given subcutaneously an equal share (24 cc.) of pooled serum obtained from five other rabbits, which 48 hours previously had received 100 r. of roentgen ray irradiation. One hour later each animal was given an intraperitoneal injection of two slants of the killed culture suspended in 20 cc. of gastric mucin. The interval of one hour between the administration of the serum and the inoculation was allowed to give an opportunity for the absorption of the serum. Three, or 60 per cent, survived, and two died in nine and 16 hours. Five rabbits were given serum intravenously and immediately inoculated. Except for the difference in the route of administration of the serum the technic was the same as that described above. One died while the serum was being given and before inoculation and, therefore, was discarded. Of the remaining four, two, or 50 per cent, survived, and two died. The deaths occurred in 16 and 22 hours. Five animals used as controls for both groups died within ten hours.

It should be noted that the animals which received the serum and failed to survive lived longer than the controls.

To control the interpretation of the results of this series of experiments the same experimental procedure was carried out in six rabbits using normal serum for the subcutaneous injections in place of serum from irradiated animals. Two, or 33.3 per cent, survived, and four died. The fatalities occurred in nine, nine, 11, and 20 hours. There were three rabbits used as controls, and all of them died within nine hours. Although there were only one-half as many survivors in this series as in those in which serum from irradiated animals was used, it is significant that one-third of the animals did survive.

Combined Roentgen Ray and Sulfanilamide Therapy.—When it evolved that the killed culture was as lethal as the living one, the failure of sulfonamide therapy became understandable. But after the effectiveness of roentgen ray irradiation became apparent it seemed probable that these two agents might supplement each other and increase the number of survivors. For this reason the following study was made: Ten rabbits were given 100 r. of roentgen ray irradiation, and 48 hours later were inoculated with the live culture. Four of them received no further treatment, but each of the remaining six was given 0.5 Gm. of one of the two sulfonamides (sulfanilamide and sulfathiazole, three each) in the inoculation fluid. Two, or 50 per cent, of those which received only irradiation survived, while two, or 33.3 per cent, of those which received both irradiation and chemotherapy survived. The fatalities occurred within ten hours. There were two controls. Both died within eight hours. Although this is too small a series for more than a relative comparison, it is obvious that the survival record was not improved by the addition of sulfonamide therapy.

Diphtheria Toxin.—All studies, thus far, pertain to one certain culture, alive and killed endotoxin. There arises, therefore, the question of specificity of roentgen ray irradiation for this particular culture and its toxin. As an effort to answer this question a study of the effect of prophylactic irradiation

upon rabbits inoculated with diphtheria toxin* was made. Diphtheria is representative of exotoxins. Its minimal lethal dose for guinea-pigs had been established in the donor's laboratories. This dosage was found to be consistently lethal for rabbits. With this toxin prostration developed more slowly and the animals survived much longer than did those which received the killed culture. The average survival period was 52 hours.

To determine the direct influence of irradiation, 16 rabbits were given 100 r. of roentgen ray irradiation, and 48 hours later the diphtheria toxin in 2 cc. of water intraperitoneally. Ten, or 62.5 per cent, completely recovered. The average duration of survival of the six that died was 61 hours. Twelve rabbits used as controls and inoculated at the same time, all died. The average survival period was 50 hours.

It is planned to determine the influence of peritoneal fluid and blood serum from irradiated animals upon this toxin, as was done in the experiments with the killed culture. These studies are in progress.

DISCUSSION.—Although this study was suggested by a clinical problem it is reported in terms of factual data as observed in rabbits. From this data no direct clinical implications are justified, and none are intended.

As stated previously, it was the purpose of the original problem to determine the effect of the sulfonamide drugs and of roentgenotherapy upon peritoneal infections produced by several different micro-organisms acting both alone and in combination. But this problem was abandoned for the one reported above, after it was learned that the first culture used was as lethal after it had been killed as it was alive, and after the unexpected finding that preliminary roentgen ray irradiation of the animals reduced the mortality from this culture both killed and alive.

Three cultures of hemolytic *E. coli* were obtained from different sources and only one proved to be pathogenic for rabbits. This culture produced within two or three hours profound prostration, which was accompanied in all of the five animals in which blood studies were made by hypoproteinemia and hemoconcentration. Because this state of shock developed so soon, and progressed to a fatal termination so rapidly, following the administration of the killed as well as the live culture, it seems reasonable to assume that death resulted from profound toxemia. Granting this assumption, it follows, then, that the culture contained a lethal quantity of toxin at the time it was injected into the animals. Consequently, any further production of toxin or other lethal factor as a result of growth of the bacteria in the peritoneal cavity was superfluous. If, therefore, the action of the sulfonamides is bacteriostatic, the cause of failure of these drugs to influence the course of events is obvious. This may be the explanation of some failures of these drugs in clinical cases.

When it was discovered that some of the animals which had received roentgen ray irradiation 24 hours to five days before inoculation with the

* This toxin was provided through the courtesy of Eli Lilly and Company.

live culture had recovered, it was thought that recovery might be attributed to the inflammatory reaction of the peritoneum caused by irradiation. This explanation, however, was invalidated subsequently by the observation that preliminary irradiation resulted in an equal number of survivors among the animals given the killed culture. Thus irradiation in some manner lowered mortality from toxemia.

These findings gave rise to the question of mechanism. Did the local inflammation of the tissues incited by irradiation interfere with absorption of the toxins or did the tissues develop some factor capable of neutralizing the toxins? Was the protective factor a local one, present only in the tissues which had been irradiated, or was it a generalized one? It had been observed that the peritoneal fluid was always increased in quantity within a few hours after irradiation. It seemed probable that this fluid might contain a factor capable of neutralizing the toxin and so, 48 hours after irradiation (the optimal period), the peritoneal fluid was aspirated along with the saline used to wash it from the peritoneum. When these washings were mixed *in vitro* with a lethal dose of either the killed or live culture the toxins were sufficiently augmented in each instance to render them incapable of killing the animals. Peritoneal washings from nonirradiated rabbits did not exert this influence.

Since the same augmentation was obtained from an admixture of the live and the killed culture and serum from animals irradiated 48 hours previously, it is apparent that whatever the product resulting from irradiation, it was present in the blood stream and thus generally disseminated. Because one out of four animals survived after receiving a mixture of normal serum and the killed culture, it appears that some rabbits' serum may normally contain the augmenting factor, or that the survival of this animal and, in part, the survival of those which received serum from irradiated animals resulted from the beneficial effect of serum upon shock.

When serum from irradiated animals was given intravenously or subcutaneously prior to intraperitoneal inoculation, the survival record was slightly more than 50 per cent, a better record than that obtained from normal serum used in the same way. It is interesting that the results from the use of serum from irradiated animals are comparable to those obtained in the animals which were inoculated 48 hours after they had been irradiated.

The effect of irradiation given 48 hours prior to the intraperitoneal injection of a lethal dose of diphtheria toxin was determined for the dual purpose of reevaluating with another toxin the observations made thus far, and of determining how specific was the antitoxic factor which resulted from irradiation. A survival record of ten out of 16 rabbits so treated is indicative of the presence of a nonspecific antitoxic substance.

CONCLUSIONS

As an attempt to explain these observations the following theory is offered as a mere suggestion. Roentgen ray irradiation caused injury to

the tissue cells. In response to this insult the cells or some group of cells liberated a protective or antitoxic factor.

Whatever the nature of the protective mechanism, time was required for its development. It was present 24 hours after irradiation—how much earlier is a problem which will be investigated. It apparently developed too slowly, however, to be of benefit to the rabbits which received irradiation after they were inoculated. It reached its peak of effectiveness in 48 hours, and by the seventh day it apparently had been entirely dissipated.

This investigation has given rise to many questions for further study; questions of optimal and minimal dosages of roentgen ray irradiation, the effect of irradiation of portions of the rabbit's body other than the abdomen, and the reaction to irradiation in other animals, *etc.*

THE OPERATIVE REPAIR OF MASSIVE RECTAL PROLAPSE*

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PROLAPSE of the rectum varies in degree from the minor cases in which only the mucous membrane of the anal canal or lower rectum is prolapsed, to the instance of massive prolapse in which the prolapse assumes enormous proportions and includes all the coats of the rectal wall. In the three cases we are reporting, the prolapse started in childhood and had gradually increased in size until it occurred not only during defecation, but also when the patient walked about. In two patients the prolapse assumed such magnitude as to constitute a major disability at age 26. The third case was able to carry on until age 42. It is noteworthy that these patients suffered a progressive increase in the size of the prolapse over many years. In none of the three patients was the prolapse less than six inches in length (Fig. 1).

On examining these patients, the most outstanding observation was that the lumen of the rectum presented on the posterior quadrant of the prolapsed mass. The long axis of the lumen was at right angles to the long axis of the body (Fig. 2). In Figure 2 the cork in the lumen indicates the site and direction of the canal. This led to the conclusion that the prolapse was more at the expense of the anterior than the posterior rectal wall. The prolapsed mass was resonant on percussion, and, on occasions, gurgling was heard during attempts at reduction. After reduction of the prolapse, the anal sphincter was so stretched that it very poorly closed the anal canal, but in two instances one could see the patient was able voluntarily to contract it. In Case 3 there was no visible evidence of the patient's ability to do so. In two cases there was a definite sulcus about three-quarters of an inch long between the anal canal and the prolapse. In Case 1 no such sulcus was present, the prolapse being so complete that the anal canal was everted. Moschcowitz¹ made an important observation: "If, after reducing the prolapse, the patient strained while the examining finger is pressed anteriorly in the lower rectum, the prolapse would not recur, whereas if pressure were made posteriorly the prolapse recurred immediately."

The disability which these young individuals suffered was very great, not only economically but socially. The problem which they presented to the surgeon demanded careful consideration. Moschcowitz's¹ article published in 1912, 30 years ago, advanced the suggestion that a massive rectal prolapse resulted from a sliding hernia of the anterior wall of the rectum at the level of the cul-de-sac of Douglas or rectovesical pouch. Our interest in sliding hernia of the sigmoid² led us to consider seriously this hypothesis. Yet if this be the correct etiology, the treatment suggested by Moschcowitz of

* Read before the American Surgical Association, Cleveland, Ohio, April 6-8, 1942.

plicating the peritoneum of the cul-de-sac of Douglas or rectovesical pouch is inefficient. It would be comparable to plicating the sac of an inguinal hernia without removing it and without any attempt at repairing the defect in the wall.

The injection treatment suggested by Gabriel is comparable to the injection treatment of an inguinal hernia, were one to dispense with the pressure of a truss during the course of treatment. If our observation be sound, that

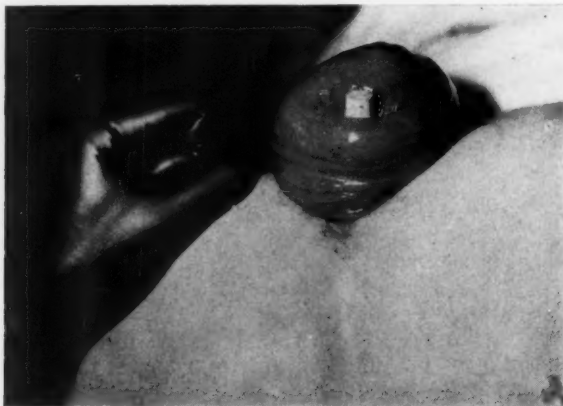


FIG. 1.—The size of the prolapse can be compared to the size of an adult fist.



FIG. 2.—With the patient in the knee-chest position the prolapse is seen from behind. The position and direction of the lumen of the rectum is indicated by the cork placed in the lumen.

the prolapse occurs at the expense of the anterior rather than the posterior rectal wall, which is very little disturbed, then the procedure of Lockhart-Mummery and Pemberton is unsound. Their technic is aimed at the fixation of the posterior rectal wall, which is little altered from its normal relationship to the sacrum.

The fact that after reduction of the prolapse, pressure anteriorly by the examining finger in the rectum prevented its recurrence even with straining, was the most important single observation confirming the hypothesis that the lesion was essentially a sliding hernia of the anterior wall of the rectum (Fig. 3).

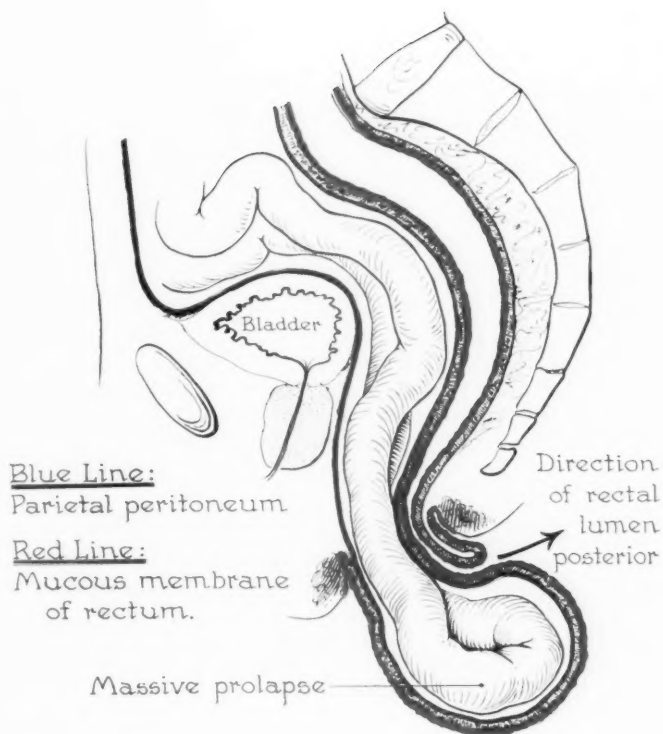


FIG. 3.—The invagination of the anterior rectal wall into itself and through the anal canal separates the fascial and muscular supports of the rectum and by overstretching results in incompetence of the anal sphincter. The lengthening of the mesentery of the small bowel occurs over the years to such a degree that small bowel lies within the hernial sac of a massive prolapse.

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In this mechanism the natural defect in the pelvic fascia which permits the passage of the rectum through the pelvic diaphragm is enlarged by the contents of the cul-de-sac of Douglas or rectovesical pouch pressing downward into the anterior rectal wall. This increased bulk of rectum further separates the levator ani by stretching the pelvic fascia, which normally unites them medially. This likewise decreases the normal fixation of the rectum at this level. The separation of the levators permits sufficient anterior wall of the rectum to be invaginated into the lumen of the rectum that the latter pro-

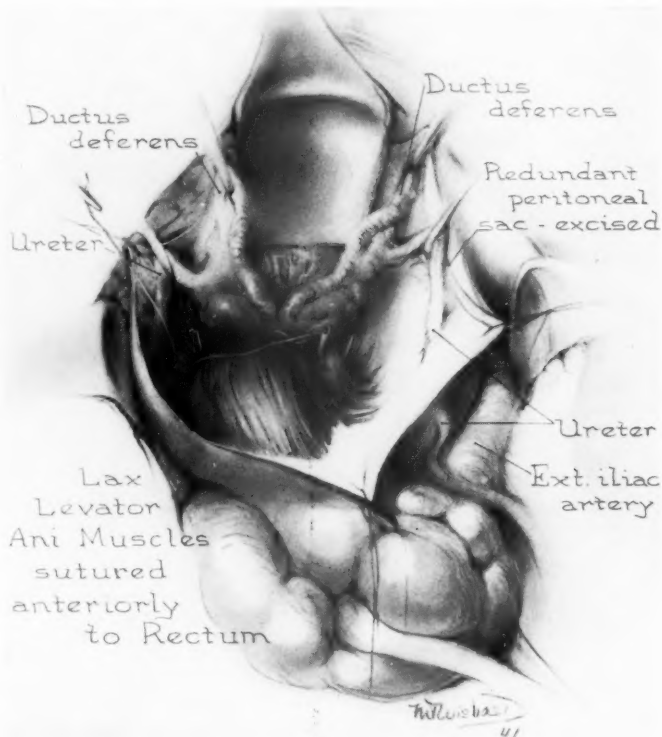


FIG. 4.—The dissection completed identifies the ureters, the seminal vesicles and the separated levator ani muscles identified by the sutures. They, with the overlying fascia, are approximated with locked mattress sutures of silk. This closure in one case was reinforced by a strip of fascia lata suture.

trudes through the anal canal. As this occurs, the course of the rectum is straightened and the normal angulation of the rectum at the level of the pelvic floor is eliminated. The posterior wall of the rectum is carried forward from the hollow of the sacrum, making the rectum now almost a straight tube, with the fascial supports most inefficient, due to the overstretching. Over the years there has also occurred elongation of the mesentery of the small bowel, permitting the latter to lie in the hernial sac, and this accounts for the tympanitic note on percussing the prolapse, as well as explaining the gurgling which was elicited on attempts at reduction.

This conception of the mechanism of production of massive rectal prolapse is not new; nor was it new with Moschcowitz, as it was first propounded

by Jeannell, in 1890. This conception, however, appealed to us so strongly that we felt it pointed a way to safe and adequate treatment, using the same principles as are applied in the operative repair of all herniae, particularly sliding herniae.²

If this conclusion be correct, then the adequate treatment should be removal of the sac and repair of the anatomic defect in the wall. The anatomic defect is in the pelvic fascia, just as in a direct inguinal hernia the defect is in the transversalis fascia. Hence, we must restore the normal relationship of the pelvic fascia to the rectal wall, as well as obliterate the peritoneal sac.

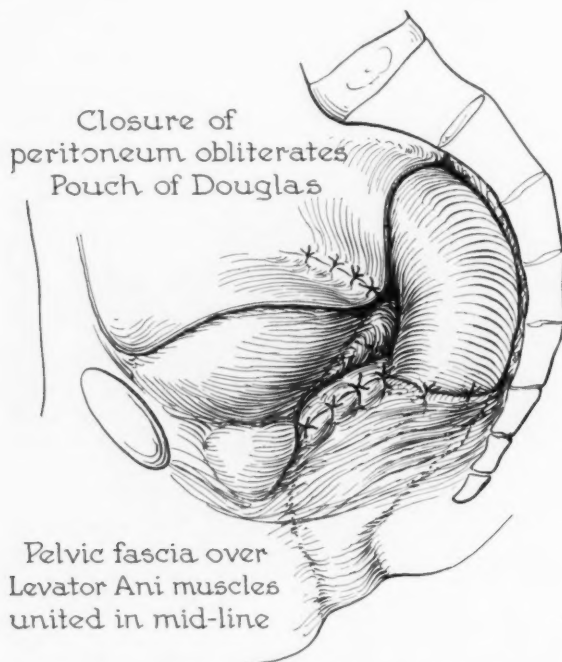


FIG. 5.—The levator ani muscles are approximated and their fascial covering united to the rectum by interrupted silk sutures. This may be reinforced by sutures of fascia lata. This approximation of the levators replaces the rectum in its normal relation to the hollow of the sacrum and prevents the prolapse. The redundant peritoneum of the pouch of Douglas is excised, and on closing the posterior parietal peritoneum the pouch of Douglas is obliterated.

To achieve this, it becomes imperative that we open the peritoneal cavity. The following are the details of the operative procedure (Fig. 4): With the patient in the Trendelenberg position, under spinal anesthesia, the abdomen is opened by a large incision displacing the lower left rectus laterally. The small bowel is packed off with hot sponges. Two points were noted: First, there was an unusually deep cul-de-sac of Douglas or rectovesical pouch; second, an unduly mobile rectosigmoid, due to the fact that the rectum was pulled forward, had a mesentery throughout the greater part of its length, and did not lie as is usual in close contact with the sacrum. Gauze on the

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end of a sponge forcep placed on the bottom of the cul-de-sac of Douglas or rectovesical pouch, with downward pressure readily invaginated the anterior rectal wall into the rectal lumen. The defect in the muscular pelvic floor could readily be palpated. This invagination was easily carried through the anal canal, and reproduced the massive rectal prolapse, and convinced us that it really was due to a sliding hernia of the anterior wall of the rectum. Furthermore, this prolapse was readily reduced by upward traction on the rectosigmoid junction. Having convinced ourselves of these facts, the peritoneum of the cul-de-sac of Douglas or rectovesical pouch was opened and dissected free from the extraperitoneal fat and areolar tissue. The ureters were then identified and surrounded with tape, in order to retract them laterally. A further dissection of the perirectal fat made possible the visualization of the seminal vesicles and the widely separated fascial-covered medial borders of the levator ani muscles. With the rectum pulled well up into the abdomen, and starting just behind the prostate, interrupted locked mattress sutures of silk were placed in the fascia covering the levator ani muscles. These sutures united the levators until their resultant approximation forced the rectum back into the hollow of the sacrum (Fig. 5). In Case 3 this repair was reenforced by a single suture of fascia lata. This maneuver restored the normal angulation of the rectum. It was then no longer possible to invaginate the anterior wall of the rectum through the anal canal. Pressure exerted at the level of the rectum and new pelvic floor forced the rectum into the hollow of the sacrum, not toward the anal canal. Interrupted silk stitches then united the lateral rectal wall to the fascia over the right and left levators (Fig. 5). This appeared to give a very adequate support to the rectum, particularly to its anterior wall, which is so important in preventing a recurrence of the massive prolapse. Excision of the redundant hernial sac and suture of the pelvic peritoneum obliterates the cul-de-sac of Douglas or rectovesical pouch entirely. The abdomen is then closed without drainage.

On return to the ward, the patient remains recumbent, with the foot of the bed elevated ten inches, for one week. A low-residue diet is given. Every effort is made to prevent a stool for a week to ten days, at the end of which time oil enemata are usually effective in producing a stool. The patient is encouraged to practice contraction of the overstretched anal sphincter many times a day, in order that it will regain its tonicity. The following are the details of the three cases:

CASE REPORTS

Case 1.—Hospital No. A64821: W. J. P., male, age 26. Admitted April 12, 1939. Mass first present at age six, gradually increased in size, and recently appeared with slight straining when patient was erect. The mass had to be replaced by manipulation. There was marked urgency of defecation.

Examination.—The mass was as large as a man's fist, and could be prolapsed voluntarily. In the knee-chest position it could be replaced by violent movements of the abdominal muscles. No ulceration was present. There was no sulcus at the anal sphincter, as the anal canal was also prolapsed. The mass was tympanitic on percussion,

and the lumen of the rectum pointed backward. With a finger in the rectum, pressure anteriorly controlled the prolapse.

Operation.—April 24, 1939: Primary healing. Discharged May 16, 1939. Has had no further trouble, and is doing hard physical work in a tannery at the present time.

Case 2.—Hospital No. A82662: W. B., male, age 42. Admitted April 4, 1940. Prolapse first noticed at age eight. Now comes down with stool and has to be replaced. The size has increased markedly in the previous five weeks. Now has a mass 6x8 inches protruding from anus, and reduction becoming difficult (Fig. 1).

Examination.—Well nourished; sphincter contraction visible and surprisingly good tone. The mass is difficult to replace. There is no ulceration and no hemorrhage. The lumen points posteriorly. The mass is resonant on percussion (Fig. 2). With a finger in the rectum, pressure anteriorly controlled the prolapse.

Operation.—April 12, 1940: Had slight superficial wound separation due to coughing from a respiratory infection. Good recovery. Complete relief, with a very slight prolapse of one area of anal mucous membrane on straining. At present is working in munitions plant as a laborer.

Case 3.—Hospital No. A99554: G. T., age 26. Admitted April 1, 1941 to the Neurologic Service, with headaches, fainting attacks, and a multiplicity of complaints. Only organic finding was rectal prolapse present since childhood. Had to be replaced after each stool. Marked increase in size of prolapse during past five years, becoming difficult to replace, and on admission prolapse occurs on walking or any exertion.

Examination.—Sphincter lax. No evidence of contraction could be demonstrated by the patient. On straining, the rectum prolapsed at least six inches; a sulcus is present between the anal canal and prolapse about one-half inch deep. By introducing two fingers into the rectum and pressing anteriorly, the prolapse could be prevented as the patient strained. Pressing posteriorly into the hollow of the sacrum while the patient strained, permitted recurrence of the prolapse.

Operation.—May 10, 1941: Bowels moved on tenth day. Primary union. Discharged.

Progress.—No further prolapse of the bowel. Slight prolapse of mucous membrane treated by injections of 2 cc. phenol and almond oil. Some difficulty in controlling stool for four months. At present has perfect control of bowel movements. On examination, the tone of the sphincter ani is remarkable, but not as strong as normal. Her neurologic symptoms have nearly all disappeared. She is working in our hospital as a ward aid at the present time. We are indebted to Dr. Keith Welsh for the privilege of seeing and reporting this third case.

CONCLUSIONS

(1) Massive rectal prolapse is a sliding hernia of the anterior rectal wall through the anal canal.

(2) The lumen of the rectal canal points posteriorly as the prolapsed mass is formed largely at the expense of the anterior rectal wall.

(3) This results in an overstretching of the pelvic fascial supports of the rectum.

(4) With the examining finger in the rectum, the prolapse can be controlled as the patient strains if pressure be exerted anteriorly, whereas if pressure be exerted posteriorly, the prolapse will recur.

(5) The treatment of this condition should be planned to apply the basic principles underlying the treatment of all herniae—first, remove the sac; second, restore the defect in the wall.

(6) A procedure is presented which fulfills these requirements.

(7) It has been successfully carried out on three patients. Two have returned to hard labor; the third is working as ward aid in our hospital.

(8) The return of tone in the anal sphincter is most remarkable.

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- ² Graham, R. R.: The Operative Repair of Sliding Hernia of the Sigmoid. ANNALS OF SURGERY, **102**, No. 4, 784, October, 1935.

DISCUSSION.—DR. VERNON C. DAVID (Chicago): Doctor Graham has limited his discussion to the type of prolapse of the rectum in which the anus, including the patulous sphincter muscles, prolapses with the four to six inch tube of bowel carrying with it the cul-de-sac of Douglas. In principle, the treatment he advocates requires an abdominal approach, opening of the cul-de-sac, and the approximation of the levator muscles by suture in front of the rectum. He is to be congratulated on the results in the three cases he reports.

To present a slightly different viewpoint, I should like to point out that the levator muscles, which have a very delicate fascial covering, completely encircle the rectum and their highest or superior surface is at about the level of the sacrococcygeal junction. To tighten these muscles by suture *via* the abdominal approach in the depth of the pelvis is a difficult procedure, and I should like to ask Doctor Graham if he finds it necessary to cut the triangular ligaments of the rectum, which lie below the culdesac, before he reaches the levator muscles. When the levator muscles are divided, as in removal of the rectum posteriorly, the rectum is still firmly anchored in place by the fascia propria, which is a dense fascia about one millimeter thick, firmly attached to the sacrococcygeal junction posteriorly and anteriorly to the prostate which it completely envelops. Before the rectum can be mobilized this fascia must be cut.

It is my belief that it is not only the atrophy and weakness of the levator muscles and depth of the cul-de-sac which favor this type of prolapse but more particularly a weakness and stretching of the fascia which allows the rectum to completely prolapse carrying the cul-de-sac with it. In repair of this type of prolapse we, therefore, believe that the structures in most need of support are in the prolapsed segment of bowel and on its outer surface, namely, the fascia propria and levator muscles. We also believe that the atonic sphincter muscles, which have been greatly dilated by the prolapse of the bowel and levator muscles through them, are a factor which favors early recurrence of the prolapse.

With these anatomic facts in mind, I should like to call your attention to the operation for the repair of this type of prolapse originally proposed by Delorme, in 1890, and first carried out by Rehn, in 1896. This operation is easily carried out under novocain anesthesia and consists in the removal of the mucosa of the prolapsed segment from the mucocutaneous line to the apex of the prolapse. The muscularis of the bowel, levator muscles, and fascia propria in the outer layer of the prolapse are collapsed like a closed accordion by longitudinal puckering-stitches, which reduces the prolapse and makes tighter the supporting levator muscles and fascia propria and places the puckered mass of muscle and fascia above the sphincter muscles, which are narrowed below it by angulating stitches. The excess of freed mucosa is then cut off and the cut surface sutured to the skin. This operation accomplishes everything but obliteration of the cul-de-sac. I first saw Doctor Bevan perform this operation, and I have carried it out in 12 cases, with good results, and no massive recurrences. In women, where the perineal body is gone and the levator muscles are widely separated, it is advisable to perform a later perineorrhaphy.

This type of prolapse demands, essentially, strengthening of the pelvic fascia and levator muscles. In my opinion this may be best accomplished by the abdominal operation described by Bardenheuer, Moschcowitz, and Graham, or by the Rehn-Delorme operation from below.

DR. CHARLES G. MIXTER (Boston): Massive rectal prolapse, particularly of the recurrent variety, is frequently a discouraging lesion from the surgeon's viewpoint. Doctor Graham has presented to us a well-conceived operation that has been successful in the

three patients he has subjected to this procedure, and in skilled hands it should yield good results. It is, however, a procedure of considerable magnitude. The lesion occurs many times in the aged and, perhaps, enfeebled group. It might not be amiss to bring before this Association briefly a simple procedure that has yielded satisfactory results in the two cases upon whom I have had the opportunity to try it.

The abdomen is opened through a low left rectus muscle-splitting incision. A small opening is made in the pelvic floor on either side of the rectosigmoid. The rectum is mobilized by blunt dissection and cigarette wicks are inserted to stimulate fixation of this bowel segment by resultant fibrosis. The wicks are brought out through stab wounds above the inguinal ligament on either side. Further experience may prove this step to be unnecessary. The sigmoid which is usually redundant is brought out of the abdominal wound in a manner similar to a subcutaneous loop-colostomy or precolostomy. The distal limb of sigmoid should run tautly downward from the lower angle of the wound to the rectosigmoid. The proximal sigmoid reenters the abdomen at the upper end of the incision. All layers of the abdominal wall except the skin and superficial fascia are closed in a routine manner beneath the exteriorized sigmoid through an opening established in the mesentery. The fat is separated from the anterior rectus sheath and allowed to gape to accommodate the loop and the skin is closed over the bowel. Care must be taken not to constrict the lumen where the bowel enters and leaves the abdomen.

Two cases, both having had three previous procedures, have been treated by operation based on the principle of fixation of the sigmoid in the abdominal wound. In the first case, a woman of about 40, a double-barrel colostomy was done, the bowel later opened, the spur crushed and the colostomy closed. This patient has remained free of recurrence and with satisfactory bowel function for two and one-half years. The second case was a rather feeble woman in the late sixties, who was operated upon by the method outlined above. She had no difficulty in moving her bowel postoperatively. It is now about nine months since operation, and I understand she has had no recurrence, though I have not had an opportunity to examine her personally.

The results in two cases are insufficient to draw conclusions from, but suggest that this simple procedure may be worthy of further trial, particularly where relief must be given in the poor-risk group.

DR. JOHN PEMBERTON (Rochester, Minn.): Since Doctor Graham mentioned the operation that I described four years ago, I would like to run over, very briefly, the principles of it, which are similar to what Doctor Mixter has described.

I think the fundamental principles of rectal prolapse are about the same that you see in the colostomy. If the distal segment or the segment just distal or just proximal to the colostomy is fixed, you will not get a prolapse of the colostomy, if you get up close to the descending colon, but if you take it in the middle of the sigmoid, then you are very likely to get a prolapse.

You cannot make a complete fixation of the rectum unless you divide the pelvic peritoneum, so this is done either on one side or both sides. Then the rectum is freed up from the segment going down there. This permits fibrosis to take place here, which you can readily determine by examining the rectum digitally after incision. This is freed up, and we get a space between the rectal wall and the sigmoid, until it heals. The problem is, of course, to suspend the sigmoid afterward. The suspension will not hold, but if it holds temporarily, for a couple of weeks, I believe the fixation will hold up.

Four years ago I reported six cases that we had operated upon. I think the longest case was two or three years. Since then we have done others, but of those six cases I know that one has had some recurrence of the prolapse.

DR. ROSCOE R. GRAHAM (closing): I have just one thought, and that is to state our amazement at what happened at the anal sphincter. In the patient whom you saw in the moving picture there was no visible evidence, whatsoever, that the patient could make the slightest contraction of the anal sphincter. That was a year ago. At the present time, by encouraging her to voluntarily attempt contraction, she has an anal sphincter which is not as good as normal but is amazingly good in its grip of the examining finger. The other two men had visible evidence at the time of operation, and they have come back with exercise in a way that is remarkable. While one is conscious of the fact that this is a major procedure, it also is undertaken to correct a very major disability.

TESTS OF HEPATIC AND PANCREATIC FUNCTION IN THE DIFFERENTIAL DIAGNOSIS AND PREPARATION OF PATIENTS WITH LESIONS OF THE BILIARY TRACT*

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THE VITAL RÔLE of the liver in the formation of prothrombin is indicated both by animal experiments and by clinical studies. Thus, Smith, Warner and Brinkhous¹ observed a precipitous fall to less than 10 per cent of normal within 24 hours after chloroform anesthesia, and a return to normal after six days. Warner² removed about two-thirds of the liver of the rat and noted a lowering of the plasma prothrombin, followed by recovery as the hepatic tissue regenerated. Warren and Rhoads,³ and Andrus, Lord and Moore⁴ independently performed total hepatectomy in dogs and found that the plasma prothrombin fell progressively to levels almost too low to measure after 12 to 16 hours. The latter authors also demonstrated that even massive doses of vitamin K were ineffective in elevating the plasma prothrombin of the hepatectomized dog. More recently, Brinkhous and Warner⁵ have confirmed the ineffectiveness of the vitamin after chloroform intoxication.

Bollman, Butt and Snell,⁶ studying chronic hepatic injury produced in rats by means of carbon tetrachloride vapor, were able to demonstrate depression of the plasma prothrombin levels as well as the failure of vitamin K to bring about improvement. These authors also noted that a diet rich in carbohydrate delayed the onset of hepatic damage and prolonged the lives of the animals by as much as 50 per cent.

Many observers⁷⁻¹⁴ have stressed the fact that the level of the plasma prothrombin is depressed in patients with hepatic disease and that under such circumstances the response to vitamin K therapy is inadequate or even absent. As yet, there is no correlation between the type of hepatic damage and the response to the vitamin, but most workers are in agreement as to the fundamental connection and as to the increase in the response as the condition of the liver improves.

These facts have suggested the use of the level of the plasma prothrombin and its response to vitamin K as an index of liver function. Thus, Pohle and Stewart,¹³ in 1940, were the first to publish experience with such a method, suggesting specifically the response of a depressed level of plasma prothrombin as measured by Quick's test to the administration of vitamin K and bile salts by mouth as a satisfactory method. In their series of 46 jaundiced patients with reduced plasma prothrombin, 28 showed satisfactory response while in 18 the level failed to improve. Wilson¹⁵ put forth the idea

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This study was carried out under a grant from the John and Mary R. Markle Foundation.

that the level of the plasma prothrombin might be considered as an index of hepatic function, and in 36 cases found a close correlation of this value with the results of the hippuric acid test.

However, both the above methods are subject to certain errors. Pohle's and Stewart's method may give inaccurate impressions because of possible failure of absorption from the intestine in the presence of disease of the digestive tract and in the rare but definite instances of defective absorptive mechanisms. Wilson's employment of the level of the plasma prothrombin fails to take into account the other factors aside from liver damage which may cause lowering of the prothrombin level.

Since October, 1939, we have studied the application of the level of plasma prothrombin and its response to intramuscular 2-methyl-1, 4-naphthoquinone as a measure of liver function in some 86 cases, and with certain restrictions find it perhaps the most accurate method available. We prefer the parenteral route—intramuscular in all our own cases—for the reason that we have encountered at least two otherwise normal individuals in whom, despite the presence of bile in the intestine and apparently normal liver function by several tests, the plasma prothrombin was depressed to about 60 per cent of normal and could not be elevated by vitamin K administered by mouth with or without bile salts. Intramuscular injection was followed by a prompt elevation to normal. This we can only explain by postulating a defective absorption from the intestinal tract.

We, therefore, have adopted the thesis—which is well borne out by clinical data to be presented below—that the level of the plasma prothrombin if below 80 per cent in a given case is an index of the performance of the liver, while the response to 2 mg. of 2-methyl-1, 4-naphthoquinone administered intramuscularly indicates whether any depression of this function is or is not due to organic liver disease.

We have compared this method with the galactose tolerance, hippuric acid and bromsulfalein clearance tests in three groups of selected cases. In a group of seven patients with Laennec's type of cirrhosis of the liver the plasma prothrombin failed to rise by more than 6 per cent after the intramuscular injection of 2 mg. of menadione. This failure to respond, we feel, indicates intrahepatic disease of a significant degree, but prognosis is only possible when the test is employed on several occasions and the trend observed. The galactose tolerance test was used in six of the seven patients with cirrhosis of the liver, and was abnormal in only four. The hippuric acid test was less accurate than the galactose tolerance test, being below 100 per cent (3 Gm.) in only two out of five of the cases. The bromsulfalein test stood last in point of accuracy with three normal results in three cases of cirrhosis.

In a group of nine cases with catarrhal jaundice the plasma prothrombin test showed impaired hepatic function in seven instances, and in general paralleled the severity of the disease. The galactose tolerance test was equally accurate in this group, showing greater than 3 Gm. excreted in seven out of nine patients. The hippuric acid test was abnormal in three out of seven

cases, while the bromsulfalein test was abnormal (10 per cent retained) in one case of catarrhal jaundice proved at operation, in which the other three tests were normal.

The third group of patients studied suffered from obstructive (extrahepatic) jaundice due to a variety of lesions. The plasma prothrombin response was good in all of 11 cases in which it was used, while the galactose tolerance test was normal in only six out of nine cases. The hippuric acid test was normal in seven out of eight, and the bromsulfalein test was normal in all four cases in which it was used. In this group of patients with extrahepatic jaundice the question arises as to whether the impairment of hepatic function as determined by the galactose tolerance test is or is not significant. If significant, then the plasma prothrombin test is less sensitive in this group than the galactose tolerance test. It seems clear that the bromsulfalein test was the least sensitive in each of the three groups of cases and that the plasma prothrombin and galactose tolerance tests yield the most significant results. The hippuric acid test falls between the galactose tolerance test and the bromsulfalein test in point of accuracy.

An important application of liver function tests is in the field of differentiation between obstructive jaundice of intrahepatic and extrahepatic origin. Such differentiation is frequently possible because the intrahepatic lesions causing jaundice, such as catarrhal jaundice, cirrhosis, *etc.*, are associated with liver damage, whereas in obstructive jaundice due to choledocholithiasis, injection and edema of the common duct or tumors of the pancreas the liver is usually normal unless the jaundice is of long standing. A wide variety of tests have been used to this end but only a few have stood up under rigid clinical application.

The galactose tolerance test was employed by Shay and Schloss,¹⁶ and by Schiff and Senior,¹⁷ who reported excellent results, but Banks, Sprague and Snell¹⁸ found the test of no real value in the differentiation of the two types of cases. Recently Bassett, Althausen and Coltrin,¹⁹ using a modification of this test, found that 82 per cent of a group of patients with extrahepatic obstruction of the common duct had less than 20 mg. per cent of galactose in the blood 75 minutes after injection, while 81 per cent of those with parenchymatous jaundice showed blood levels above this figure. In 18, or 19 per cent of the cases, therefore, the test failed to give an accurate diagnosis.

The cephalin-cholesterol flocculation test of Hanger²⁰ has been highly accurate in the hands of its inventor, being correct in 58, or 92 per cent, of 63 cases. Rosenberg²¹ confirmed this finding, and observed that in jaundice of recent origin a strongly positive flocculation test indicated an intrahepatic origin, while a negative or faintly positive test suggested an extrahepatic cause for the jaundice. Pohle and Stewart,²² however, found the test unsatisfactory in the differential diagnosis of jaundice, as it was strongly positive in six of 23 patients with obstructive jaundice of extrahepatic origin.

Lord and Andrus²³ have used the response of the plasma prothrombin

level to menadione administered intramuscularly as a means of determining the site of origin of obstructive jaundice and obtained a high degree of accuracy. Thus, it was correct in 32 of 36 cases of intrahepatic jaundice and in 49 of 50 cases of extrahepatic obstruction of the common duct, an over-all accuracy of 94 per cent. There were 20 additional cases of extrahepatic jaundice, not included in the above group, whose initial prothrombin level was over 80 per cent, a finding which, when present in jaundice, has always indicated it to be of extrahepatic origin.

The technic employed was as follows: Determinations of the level of plasma prothrombin are made on two successive days by the Warner, Brinkhous and Smith test,²⁴ and if the two levels are within 5 per cent of each other, 2 mg. of menadione are injected intramuscularly, and the prothrombin is determined at intervals of 24, 48 and 72 hours. On the other hand, if there is a difference greater than 5 per cent in the two initial levels of prothrombin, the level is determined on the third day, and so on, until the levels on two successive days are found to be within 5 per cent of each other. When such agreement occurs, then the menadione is administered. On no occasion have we found it necessary to determine the prothrombin for more than three successive days before injecting menadione.

Lake, using a modification of the method of Agren and Lagerlof²⁵ for measuring the external secretory function of the pancreas, with intravenous secretin as the stimulus, has studied about 34 patients including a number of cases of obstructive jaundice. Agren's and Lagerlof's method has also been employed by Diamond and Siegel,²⁶ and by Pratt, Brugsch and Rostler.²⁷ The method consists, essentially, in obtaining duodenal secretion by means of a double lumen duodenal tube and, after collecting a control sample, injecting secretin intravenously. Further samples are collected ten, 20, 40 and 60 minutes later, and the total volume of secretion together with the sodium bicarbonate, trypsin, diastase and lipase content measured. The average and minimal normal values are as follows:

	Average	Minimal
Volume cc.....	203 cc.	94
Bicarbonate:		
Highest concentration.....	99.6	76 milli-equivalents
Total output.....	151	$62 \left(\frac{N}{10} \text{ NaHCO}_3 \right)$
Diastase.....	432	238 units per 60'
Trypsin.....	47	20 units per 60'
Lipase.....	12,260	6,000 units per 60'

By means of the combined use of the response of the plasma prothrombin level to intramuscular menadione and a study of the amount of pancreatic ferments in the duodenal contents, it has been possible to localize some of the lesions causing obstructive jaundice with a high degree of accuracy. The first of the following cases demonstrates the application of these tests in the diagnosis of carcinoma of the common duct not involving the ampulla, while the second indicates a possible source of error in the presence of an aberrant pancreatic duct.

HEPATIC AND PANCREATIC FUNCTION

Case 1.—N.Y.H. No. 309635: J. M., male, age 70, entered the hospital complaining of jaundice and itching of the skin of six weeks' duration. The family history and past history were noncontributory. The salient features of the present illness began six weeks prior to admission and consisted of jaundice, itching of the skin and clay-colored stools. The jaundice persisted without remission, and over the past six months there had been generalized weakness and a loss of 35 pounds in weight, with poor appetite. Bowel movements had been regular and there had been no bloody or tarry stools.

Physical Examination.—The patient was a well preserved, deeply jaundiced male who appeared acutely and chronically ill. The skin, aside from the jaundice, showed many scratch marks over the trunk. A grayish, raised area was seen on the anterior thorax in the third interspace, and over the spinous process of the third lumbar vertebra was a large sebaceous cyst 3x2x3 cm. There was no lymphadenopathy and the heart and lungs showed no abnormalities.

Abdominal examination showed the wall to be soft and relaxed. The liver was palpable 7 cm. below the costal margin in the midclavicular line, and was smooth and soft in consistency. Two large inguinal herniae extending into the scrotum were evident. The remainder of the physical examination, except for a moderately enlarged prostate, was negative.

Laboratory Data.—On admission: Urine—sp. gr. fixed between 1.012 and 1.016; albumin 2+; 8-10 W.B.C. per high power field; occasional hyaline cast. Bile pigments were present in the urine. Blood—hemoglobin, 11 Gm.; R.B.C. 3 million; W.B.C. 8,200, with normal differential. Kline negative. The B.U.N. varied from 17 to 64. Blood sugar 63; chlorides 400 on one occasion and 540 on another. The serum protein varied from 5.7 to 7.0. Icteric index on admission, 112, rising later to 187. The stools were negative for bile. G.I. series was negative. Chest film showed an elongated and tortuous aorta and slight pulmonary emphysema. The plasma prothrombin level was 38 per cent of normal on admission, falling to 18 per cent on the second day. The administration of vitamin K was promptly followed by a rise to 73 per cent, which subsequently reached 100 per cent on one occasion, and remained above 66 per cent at all times.

Studies of the pancreatic secretion showed the following:

Volume cc.....	187 cc.
Highest bicarbonate level.....	114 milli-equivalents
Total output.....	152.5 $\left(\frac{N}{10} \text{ NaHCO}_3\right)$
Diastase.....	149.7 units per 60'
Trypsin.....	34 units per 60'
Lipase.....	12,747 units per 60'

This indicated a normal response, except for a somewhat low diastase value resembling the results seen in pancreatitis.

The normal response of the plasma prothrombin level to intramuscular menadione was strong evidence that the jaundice was due to obstruction of the common duct, and the presence of normal amounts of the external secretion of the pancreas indicated patency of the pancreatic duct. The obvious diagnosis was, therefore, an obstruction of the common bile duct above the ampulla, and, at operation, a hard, nodular tumor mass was found extending from the junction of the cystic and common ducts down to the duodenum but not involving the ampulla. Cholecystojejunostomy was performed, which functioned only temporarily as bile was present in the stools for only a few days. He died on the twenty-third postoperative day, and at postmortem examination the growth was found to have extended to involve the cystic duct, thereby preventing the cholecysto-enterostomy from functioning.

Case 2.—N.Y.H. No. 311583: J. B., male, age 57, had complained of jaundice and itching for four weeks. The family and past histories were irrelevant to the present illness. This began about six months previous to his admission, when he experienced four or five episodes of epigastric fullness coming on shortly after eating, and lasting for about

two hours. Following this he had no further symptoms until about four weeks before entering the hospital when he had diarrhea for one week, passing ten to 12 stools a day, which were light in color. At this time his appetite became poor and he began to note the yellowish discoloration of his skin. The jaundice deepened steadily and was associated with itching, dark urine and clay-colored stools. He became more easily fatigued, and lost 20 pounds in weight.

Physical Examination.—The patient was well-developed and well-nourished, deeply-jaundiced, and in obvious distress because of itching of the skin. The positive findings centered in the abdomen, where a mass was felt in the upper quadrants which extended about five fingers' breadth below the right costal margin. This was quite obviously an enlarged liver and, extending from beneath it for about 8 cm., there presented a rounded, smooth, nontender mass representing an enlarged gallbladder.

Laboratory Data.—On admission: Urine—sp. gr. 1.012 to 1.020. Blood—hemoglobin 10 Gm.; R.B.C. 3.8 million; W.B.C. 9,000, differential not remarkable. Blood chemistry: Sugar, 78; urea nitrogen, 11; icteric index, 100; serum proteins, 6.6; chlorides, 620; CO_2 combining power, 52.

The study of the pancreatic secretion from the duodenal drainage showed:

Volume cc.	501 cc.
Highest bicarbonate level.....	96 milli-equivalents
Total output.....	382 $\left(\frac{N}{10} \text{ NaHCO}_3\right)$
Diastase.....	673 units per 60'
Trypsin.....	115 units per 60'
Lipase.....	31,886 units per 60'

These results indicated an extremely active pancreatic response to secretin, much higher in all respects than the average normal values.

At operation, a tumor was found involving the second portion of the duodenum, the region of the ampulla and the inferior portion of the head of the pancreas. The head and body of the pancreas, together with the entire duodenum to a point beyond the ligament of Treitz, was resected. The remainder of the pancreas was implanted into the open end of the jejunum and an antecolic gastro-enterostomy and cholecysto-enterostomy performed. The patient has recovered and is apparently well three and a half months later.

Examination of the specimen revealed a carcinoma of the duodenum invading the pancreas and obstructing the ampulla. There was a very large accessory pancreatic duct emerging about 5 cm. proximal to the ampulla, explaining the presence of pancreatic enzymes in the duodenum.

The presence of such aberrant ducts may vitiate the accuracy of the secretin test in localizing obstructive lesions and the case (Case 2) herewith reported demonstrates the possibility of misleading results from this cause.

During the past decade, the condition of the liver has been studied in a variety of surgical diseases, such as gallbladder disease, obstructive jaundice, and hyperthyroidism, with the result that renewed interest has been directed toward factors which maintain and improve hepatic function. Coincident with these studies, there has been much clinical and experimental work on cirrhosis of the liver. Although much remains to be learned concerning the pathogenesis of cirrhosis, its prevention and treatment, and the optimal means of protecting the liver or of improving the function of the already damaged organ, significant information has been forthcoming.

Thus, the effect of anoxemia in producing hepatic damage has been demon-

strated by Rich,²⁸ and by Goldschmidt, Ravdin and Lucké,²⁹ and its clinical significance has been emphasized by Judd, Snell and Hoerner.³⁰ Selection of the proper anesthetic in patients with diminished liver function, and the liberal use of oxygen therapy during the postoperative phase, is of great importance in preventing further damage to the liver, both in conditions such as hyperthyroidism, in which oxygen requirements are increased above the normal, and in patients with pulmonary complications or anemia, which may exert anoxic effects on the hepatic cells.

The deleterious effects of mechanical trauma to the liver as reflected in the plasma prothrombin level has been demonstrated experimentally in the dog,^{31, 32} emphasizing the necessity for handling the liver as little as possible during operations.

However, most important for the prevention of hepatic damage and for the improvement in function of an already impaired liver is careful dietary management of the patient. For more than 30 years, experimental and clinical studies on the relation of various food factors to the liver have been carried out, and recently significant facts have emerged. The favorable influence of a high carbohydrate diet on the liver of rats to which chloroform had been administered and the adverse effect of fat in the diet was demonstrated by Opie and Alford.³³ Several workers confirmed the above findings, but recently Goldschmidt, and his coworkers,³⁴ observed that the proportion of fat in the liver was of more significance in its susceptibility to injury than the amount of glycogen present. They postulated that fat in the hepatic cell acts as a site of retention for the chloroform and, by fixing this circulating toxin, causes degeneration and necrosis. By increasing both the fat and glycogen content of the liver simultaneously they were able to show that such an organ was exactly as susceptible to injury as one in which only the fat content was elevated. In other words, the beneficial effects of glycogen were indirect, through displacing the fat in the liver cells and sparing protein.

The rôle of protein and its influence on the liver has been a subject of considerable controversy, but certain definite conclusions are now possible as a result of recent work by Ravdin, and his associates, and by Whipple, and his coworkers. Bollman and Mann³⁵ claimed that protein in the form of meat was almost as harmful to the survival of dogs intoxicated with repeated small doses of carbon tetrachloride as was a high fat diet, and believed that it was not the protein *per se*, but rather the water soluble extractives in meat which were the responsible agents. On the other hand, Messinger and Hawkins³⁶ found that a high protein diet (meat in the form of hamburger) was most effective in preventing hepatic injury when intravenous arsphenamine was employed as the hepatotoxin. Davis and Whipple³⁷ reported that skimmed milk and casein have a marked protective action on the liver against chloroform, while skeletal and cardiac muscle were far less effective. Goldschmidt, and his coworkers,³⁴ also submit evidence of the importance of protein in the protection of the liver against chloroform, pointing out that protein has the following four modes of action: (1) Probably some specific, and as yet un-

known action on the liver cell; (2) by displacing fat more effectively than carbohydrate, thereby making the liver less susceptible to injury; (3) through the fact that the liver is one of the chief storehouses of protein; and (4) by playing the major rôle in the regenerative phase, which begins within 72 hours of the original injury to the organ. The above authors established the fact that protein causes a decrease in the fat content of the liver better than does carbohydrate both in rats poisoned with chloroform and in dogs with obstructive jaundice.^{34, 38} Lord, Andrus and Moore³⁹ confirmed the efficacy of a high carbohydrate, high protein (milk as the source of protein), low fat diet in dogs with obstructive jaundice, demonstrating that animals on this carefully controlled diet lived an average of 75 days, in contrast to a group of dogs which lived an average of 47 days when kept on a regular balanced laboratory diet.

Miller, Ross and Whipple⁴⁰ have recently shown that methionine and cystine have a marked effect in protecting the liver against chloroform anesthesia in dogs with hypoproteinemia. They believe that the specific action of these amino-acids is due to their SH* groups which tend to spare the normal enzymes associated with the oxidation-reduction system in the hepatic cells (glutathione, etc.). It is their opinion that chloroform produces its toxic effect by injuring these enzymes, and that an excess of SH* groups as in cystine and methionine spares the cells in the presence of the toxic agent. Since the milk protein, casein, is high in these amino-acids, it seems likely that the specific effect of protein, postulated by Goldschmidt, and his co-workers, may rest on the same basis.

In addition to the above factors, the significance of total caloric content of the diet has been emphasized by Ravdin, and his coworkers,⁴¹ who found that a high caloric, general diet was of greater value in lowering the lipid content of the liver than was the intravenous administration of glucose alone. In fact, animals on the intravenous glucose regimen actually showed a small increase in the lipid content of the liver. From this study the importance of a diet adequate in caloric intake becomes evident.

Finally, perhaps the most significant findings, in the experimental work on the influence of diet on hepatic function and structure, concern the importance of certain vitamins and vitamin-like substances to the liver. Best, and his associates,^{42, 43, 44} have reported an extensive study on the effect of choline on the metabolism of fat in the liver and have shown that this substance in amounts as small as 5 mg. per day will cause a decrease in lipid content of the liver of a rat on a high fat diet, and will also prevent the deposition of fat under similar circumstances. On the other hand, these workers were unable to demonstrate that choline had any protective action against fatty degeneration of the liver of rats poisoned with either phosphorus or carbon tetrachloride, although it was most effective in clearing fat from the liver poisoned with these agents. Miller, Ross and Whipple⁴⁰ confirmed the work of Best,

* SH=sulphydryl.

and his coworkers,^{43, 44} finding that lecithin (5 Gm. per day) for three days before chloroform anesthesia, in protein depleted dogs, failed to protect the liver. Goldschmidt, Vars and Ravdin,³⁴ also, are quoted by Miller, Ross and Whipple,⁴⁰ to the effect that choline was of no value in the protection of the liver.

Forbes, Neale, and their associates,⁴⁵⁻⁴⁹ have isolated a crystalline substance from hog liver having a markedly protective action against chloroform and carbon tetrachloride in rats. They subsequently identified the substance as xanthine, and demonstrated that its action is neither on the fat content of the liver nor on the lipid level of the blood. Forbes, Leach and Outhouse⁴⁹ believe that the susceptibility to carbon tetrachloride poisoning is not related to the lipid content of the liver but rather to the active metabolism of fat in this organ.

Experimental necrosis and cirrhosis of the liver also have been produced in the rat⁵⁰ and rabbit,⁵¹ using special diets which were deficient chiefly in the B complex; Rich and Hamilton⁵¹ finding that rabbits fed a diet adequate in every respect except for the B complex developed cirrhosis of the liver in from 25 to 113 days. If all of the then known synthetic vitamins of the B complex were added, including thiamine, nicotinic acid, riboflavin and B₆ (pyridoxine), the cirrhosis still occurred. If, however, whole brewers' yeast was administered, the changes in the liver were prevented. Kensler, and his associates,⁵² using butter-yellow (dimethylaminoazobenzene) in the diet of rats have produced carcinoma of the liver in 96 per cent of the animals in an average of 150 days, but this was regularly prevented by the addition of whole brewers' yeast. However, prevention by nicotinic acid and riboflavin was accomplished only in the presence of large quantities of those two synthetic vitamins, while riboflavin and casein showed excellent protection (seven per cent of the rats). Recently, DuVigneaud, and his coworkers,⁵³ have found that the addition of biotin increases the incidence of carcinomata of the liver in rats fed butter-yellow and "breaks through" the protective effect of diets containing riboflavin, casein and choline. It is significant that cirrhosis precedes the development of the neoplastic process in these animals.⁵²

Further evidence of a protective factor in the B complex was adduced by Drill and Hays,⁵⁴ who showed that normal liver function as measured by the bromsulfalein test can be maintained in dogs when thyroid extract was administered, while impairment of hepatic function occurred regularly despite an adequate diet, unless supplemented with brewers' yeast.

Daft, Sebrell and Lillie⁵⁵ were able to produce cirrhosis of the liver in rats on a special diet and could prevent it by adding casein (30 per cent of the diet), methionine (0.7 per cent of the diet) or choline (20 mg. daily) either singly or in combination.

We⁵⁶ have studied the protective effect of a number of substances against minimal liver damage by what appears to be a very sensitive method. A description of the technic follows. Normal adult dogs weighing about 10 Kg.,

which have been kept on the regular balanced laboratory diet, are injected subcutaneously with minute amounts (0.03 to 0.24 cc. per Kg.) of chloroform dissolved in mineral oil, and plasma prothrombin determinations by the method of Warner, Brinkhous and Smith²⁴ are carried out before injection, and every 24 hours thereafter, if possible, for one week. The 24- and 48-hour samples are the most important. Although there may be a wide range in the fall in the plasma prothrombin following the injection of any given amount of chloroform—animals new to the laboratory usually show a greater fall in the level of plasma prothrombin after the injection than animals which have been in the environment of the laboratory for several months—in general, a relatively constant fall occurs from animal to animal when the same amount of chloroform is used.

Plasma Prothrombin in Per Cent of Normal

Chloroform Cc. per Kg.	Preinjection	Postinjection	
		24-Hour	48-Hour
0.03.....	100	75	80
0.12.....	100	50	60
0.24.....	100	30	< 3

Only an occasional acclimated dog shows jaundice when 0.24 cc. per Kg. of chloroform is injected, and most animals survive 0.5 cc. and 1.0 cc. per Kg. amounts. This finding is in contrast to the effects of 20 minutes of light chloroform anesthesia, as described by Miller, Ross and Whipple⁴⁰ as their standard dose, which caused jaundice and often death in the control animals. Our dosage—0.12 cc. to 0.24 cc. per Kg.—is four to six times smaller. In normal dogs,¹ 90 minutes of deep chloroform anesthesia does not usually kill the animal, although jaundice appears and the prothrombin and fibrinogen levels fall to very low levels. Barrett, and his coworkers,⁴⁴ in their experiment on the effect of choline on the liver, when carbon tetrachloride was used as the hepatotoxin, employed 0.7 to 0.8 cc. of carbon tetrachloride per rat (200 Gm.) which is approximately 30 to 40 times the amount per unit weight which we use in the dog. When we use such minimal doses we find that protein added to a well balanced diet in a normal dog is less effective in conferring added protection to the liver. Thus, casein was fed to dogs in 13 Gm. per Kg. amounts per day, for three days (the standard feeding period), with only slight beneficial effect, the treated animals showing almost as great a fall as the controls.

Attention was then directed to certain factors in the B complex. It was found that thiamine (2 mg. per Kg.), riboflavin (0.5 mg. per Kg.), and nicotinic acid (14 mg. per Kg.) were without protective effect in the doses used. On the other hand, whole brewers' yeast (1 Gm. per Kg.) was effective to a significant degree, the fall in the plasma prothrombin being cut approximately in half. Also, the return of the prothrombin to normal was hastened from seven days—the usual time for recovery—to five days on the average. Our experiments indicate that the protective action of a single dose of 1 Gm. per Kg. of brewers' yeast begins to be lost by the end of 24 hours.

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Choline was found to have a greater protective action than any other individual substance and was quite as effective as whole brewers' yeast.

		Plasma Prothrombin in Per Cent of Normal		
Chloroform 0.24 Cc. per Kg.	Experiment	Preinjection	Postinjection	
			24-Hour	48-Hour
Plus choline, 200 mg. per Kg.....	1	81	77	8
	2	93	63	24
	3	90	44	28
Plus brewers' yeast, 1 Gm. per Kg.....	4	79	77	40
	5	84	77	10
	6	87	11	< 4

N.B. Experiment started on third and last feeding day.

This may be reconciled with the results of Miller, Ross and Whipple; Best, MacLean and Ridout; and Goldschmidt, Vars and Ravdin, on the following grounds: In the experiments of Miller, Ross and Whipple, the outstanding abnormality of their dogs was the low protein content of the plasma (and presumably of the liver). Thus the agent protecting the livers of their animals was probably the SH factor of methionine and cystine. Choline was apparently of no avail in hypoproteinemic animals against such large doses of chloroform. From Table II, of Goldschmidt, Vars and Ravdin,³⁴ it seems possible that choline did exert a definite, though small protective effect, in both experiments in which it was used (Groups 8 and 17). Both Best, and his associates, and Goldschmidt, and his coworkers, have also used relatively enormous doses of carbon tetrachloride and chloroform, respectively, as compared with the amount used in our experiments.

Methionine and cystine were compared with choline and the latter found to be more effective in normally fed dogs, although the former did show a moderate degree of protection:

		Plasma Prothrombin in Per Cent of Normal		
Chloroform 0.24 Cc. per Kg.	Experiment	Preinjection	Postinjection	
			24-Hour	48-Hour
Plus choline, 200 mg. per Kg.....	1	100	68	41
	2	91	68	70
Plus cystine, 500 mg. per Kg.....	3	87	27	< 2
	4	91	73	70
Plus cystine, 500 mg. and methionine, 200 mg./Kg.....	5	95	59	66
	6	91	31	41

The exact mechanism whereby such hepatotoxic agents as chloroform and carbon tetrachloride exert their deleterious effects is not clear nor is the means whereby various factors protect against such injury entirely evident. In this connection, however, the following interesting hypothesis has been offered: The toxic agents, having reached the liver, are held there in proportion to the amount of fat present. The preponderance of central necrosis in the hepatic lobule may, perhaps, be due to the diminishing oxygen tension of the blood

and the tendency for the fats to be deposited more in this region than peripherally. The hepatotoxin then exerts its harmful effect by interfering with the normal oxidation-reduction system within the cells, involving glutathione and other SH factors. If the interference be sufficiently extensive, degeneration and necrosis result.

It is evident, therefore, that protection of the liver may be undertaken at several points. First, any factor which diminishes the exposure of the individual to the toxic agent—such as chloroform, carbon tetrachloride, phosphorus, arsphenamine, *etc.*—is of vital importance in lessening the amount which reaches the liver.

Second, any factors which lower the lipid content of the liver tend to diminish the amount of the toxic agent held in the liver. Here, a high caloric diet rich in protein, and carbohydrate and low in fat is of paramount importance, the protein for its fat-displacing action and the carbohydrate largely for its protein sparing effect and to a lesser extent, perhaps, in also displacing fat. Choline, by its marked effect in decreasing the fat in the liver, is also of considerable value at this point.

Third, all factors tending to spare the oxidation-reduction system of the cells, as for example the SH group of certain amino-acids, such as cystine and methionine, may exert a protective action. Oxygen therapy is valuable in maintaining a high oxygen content of the blood circulating through the liver sinusoid and, conversely, anemia or certain anesthetic agents associated with relative anoxia may exert a deleterious effect.

Fourth, an abundance of protein is important in enhancing the regenerative phase of the liver, and here also choline and perhaps xanthine may aid by clearing fat from the injured organ.^{44, 57}

Other protective actions as yet not clearly understood may result from such dietary measures, as it may be that such substances as choline and unknown B complex factors exert some specific action on the hepatic cell of which we are not as yet aware.

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DISCUSSION.—DR. I. S. RAVDIN (Philadelphia, Pa.): This is a very interesting paper of Doctor Andrus and his associates, and I am very happy to discuss it. The method they have used in order to improve our knowledge of the functional activity of the liver is one that is certainly in the right direction. It may well be that the determination of the concentration of prothrombin and the response they have used following the intramuscular injection, may prove to be more important from the functional point of view than any other method that is now being employed.

The problem of liver protection and liver regeneration is one that must concern all of us. If we think back now a period of 30 years, to the time when Opie and Alford published their historic paper on the protective action of certain foodstuffs against liver degeneration, and the subsequent papers published by George Whipple and his associates, and Graham and others, we can only think of the paper published by Moses and Smith in 1924, in which they questioned the diets used by the previous investigators. They pointed out that the diets which had been called carbohydrate diets were not pure diets, on the one hand, and that in many instances they were completely inadequate for growth in the animals to which they were fed.

There can be no doubt that carbohydrate has protected the liver, but there can also be no doubt that carbohydrate does not offer maximum protection. This statement was made 26 years ago by Dr. George Whipple: "Under the favorable conditions of carbohydrate diet a liver will regenerate at the rate of 100 grams of liver tissue a day."

The growth that could take place in the liver under such circumstances would have to take place from the indigenous breakdown of protein and that would be a minimum and not maximum growth.

The observations my associates have been making over a period of years pointed strongly to the fact that an adequate amount of adequate protein in the diet prevents the liver from injury. In the observation of Andrus and his associates, casein was not absent for a long time. Three days is insufficient time. Furthermore, the amount of casein in the diet must exceed 20 per cent. Under such circumstances casein will protect the liver from injury. It protects the liver from injury because at the present time it is the best available foodstuff to rid the liver of fat. It will do it twice as rapidly as will carbohydrate. Therefore, one has a minimum amount of fat in the liver after feeding period.

The second relation that has been pointed out by Doctor Andrus, and his associates, is the perhaps specific detoxicating factor we pointed out some years ago. At that time we did not know what they were, but there is certain evidence that strong components of the protein molecule directly protect the liver.

We have repeated the observations of Miller, Hawkins, and Messenger in regard to specific protective action of cystine and methionine. While cystine and methionine offer some degree of protection from a variety of these intoxications they do not offer the type of protection afforded by sterile fixation abscess with sodium arsenite or as afforded by the administration of high carbohydrate protein diet over an adequate period of time.

The problem of protection of the liver is one entirely separate from the problem of regeneration. For protection, casein is the most adequate protein. In the problem of regeneration, the matter is different. There one must provide that type of protein which contains the components most readily used for regeneration, and that protein is the lymph substance itself.

DR. ARTHUR B. MCGRAW (Grosse Pointe, Mich.): I hope Doctor Andrus will forgive me for taking advantage of his paper to comment on an aspect of this immediate program that has impressed me very much, and that is the part of his paper which dealt with the protection of the liver through the ingestion of casein, and, furthermore, Doctor Ravdin's comments following in his discussion.

When one has been thrust rather abruptly into the Naval Service and has spent three months there, one is forced very rapidly into thinking about a marked simplification of one's approach to surgical problems, and also the probable necessity for compromising to some extent the methods and means which one uses in the interest of getting things done, without, however, compromising adequacy methods or the things one has learned to know best.

These little points have come out for the protection of the liver. In the Navy we have to use chloroform below-deck; we cannot use ether. We cannot very well use local or spinal anesthesia. There was a point in Dr. Moyer's paper this morning about developing antagonistic action of ether in the use of intravenous anesthesia. There were points in Doctor Siler's paper yesterday and in Doctor Brown's paper, whereby we may be better able to treat the dozens of burns that may come upon us suddenly in an adequate way, far better than we might be able to treat one burn by an elaborate method. These things mean a great deal to a great many people. So partly as a personal thing and partly in behalf of the Service, I want to pay tribute to the helpfulness of this program which, in a superficial way, does not seem like a war program, and also to point out that only in our type of life and point of view can these applications that can be put to war surgery come out of humanitarian surgical investigation.

DR. WILLIAM D. ANDRUS (closing): I have nothing in particular to say further, except to thank Doctor Ravdin and Doctor McGraw for their discussion. I did not really mean to infer that we had any doubts as to the protective action of casein. I think Doctor Ravdin and his coworkers have amply demonstrated the efficacy of that particular substance. I think it may well be that his criticism is justified and that we did not feed the animals long enough with that particular substance. We will remember that. It does have a markedly protective action, as was shown. I believe there were some circumstances in our animals which may have prevented the appearance of that particular action.

VITALLIUM TUBES IN BILIARY SURGERY*

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STRICTURE of the common bile duct may result from congenital atresia, ulceration from stones, or infection from septic cholangitis, but most often follows clamping, ligation, or excision of the duct during an operation for cholecystectomy. The presence of structural anomalies, the occurrence of unexpected hemorrhage deep in the wound, or the distortion of normal anatomic landmarks by infection are circumstances that may confuse even the most expert surgeon, and are likely to bewilder the operator who has not been schooled in common duct surgery.

Small strictures may be successfully treated by dilatation, division, excision, and end-to-end anastomosis, or by plastic repair to enlarge the lumen. These procedures are applicable only if normal tissue can be approximated without tension for otherwise reformation of the stricture occurs. An alternative method is by implantation of the hepatic or common duct into the stomach, duodenum, or jejunum which has the two possible faults of stricture formation at the site of the anastomosis and of ascending biliary infection from lack of the sphincter of Oddi.

Long strictures from extensive loss of the common duct create a very difficult problem which may appear insoluble when multiple operations fail to correct the defect. Three years ago such a condition was encountered in a young woman, the mother of five children, who on two occasions was asymptomatic with a rubber T-tube in the duct but who reformed a stricture shortly after its removal. This led to a trial of permanent intubation of the common duct with a Vitallium tube. The patient recovered completely and her transformation from chronic invalidism to useful living was so dramatic that it gave encouragement to try the method in others. The subject was presented⁷ at the meeting of the Society of University Surgeons a year ago. Since then more information has accumulated from animal experimentation, dissection on cadavers, and clinical experience, especially with different uses for these tubes and with modification of their design. It appears desirable at this time to report these data and evaluate the use of Vitallium tubes in biliary surgery.

COMMON DUCT STRICTURES

The first Vitallium tube was made 4 cm. long, 6 Mm. wide in outside diameter with a central flange 6 Mm. high for an anchor which protrudes through the wall of the duct and prevents the tube from slipping out of place. No modification of the anchoring device has worked better than this simple flange and the only change that may be desirable is to shorten it to 4 Mm.,

* Read before the American Surgical Association, Cleveland, Ohio, April 6-8, 1942.

for sometimes it protrudes too far above the duct. Figure 1, No. 1, shows in a detailed sketch how a flat piece of metal is welded to the tube to make the anchor. This flange can be grasped with a curved clamp to allow manipulation of the tube in a deep wound (Fig. 1, No. 2), for without this it would be difficult to insert the tube into the ends of the bile duct. Figure 1, No. 3, shows how an unanchored tube may slip below the level of injury and allow reformation of a stricture. Loss of substance of the duct or fixation by scar tissue may make it difficult to bring the ends of the duct together over the tube to suture them in place. For this purpose, tension sutures pulled through the eye of the flange (Fig. 1, No. 4) can be used to hold the duct while doing the anastomosis. These can be removed after the suture line is completed or left in to take tension off the anastomosis if desired.

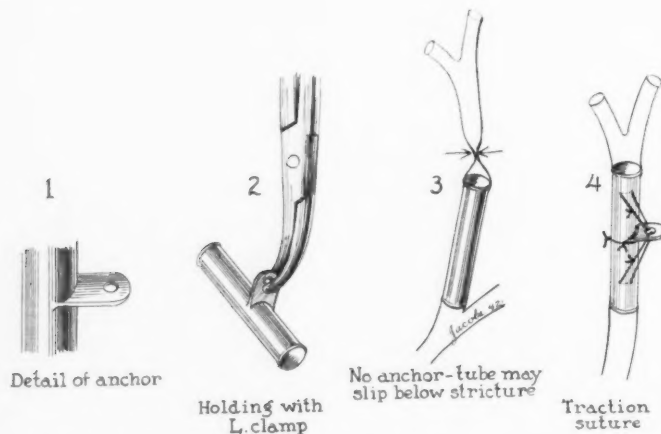


FIG. 1.—The flange on the Vitallium tube used to anchor it in place. (1) A detail sketch to show how a flat piece of metal is welded to the tube for an anchor. (2) Shows how the tube can be manipulated by a clamp grasping the flange. (3) A diagrammatic illustration of how an unanchored tube may slip down below a stricture, allowing it to reform. (4) Demonstrates the purpose of the eye in the flange for holding tension sutures while doing the anastomosis.

The majority of the cases which require permanent intubation of the bile duct have had previous operations for repair so the ends of the duct are bound together by scar tissue. This should not be excised. The normal duct should be opened above and below the stricture and the tube inserted (Fig. 2, Nos. 2 and 3). In this way the Vitallium tube holds open the strictured area and there is no danger of the ends of the duct slipping off the tube. When used for this purpose it was found that the length of the tube could be shortened from 4 cm. to 3.3 cm.

The standard 6 Mm. x 3.3 cm. tube was never designed for use in anastomosing the bile duct to the intestinal tract, in fact it was created to avoid that very thing and so preserve the function of the sphincter of Oddi. However, it has been used by others on several occasions for hepaticoduodenostomy (Fig. 2, No. 4), apparently to prevent stricture of the anastomosis. This is the only possible advantage of such use and even this may be vitiated

VITALLIUM TUBES IN BILIARY SURGERY

by the tendency of all tubes used in this way to pass into the gastro-intestinal tract.

Loss of part of the duct followed by infection and scar may leave the two ends fixed in widely separated positions. Attempts to bridge this gap by a Vitallium tube tied into each end of the duct have failed because of retraction of the duct off the ends of the tube. To overcome this, a straight tube 6 cm. long was made but it was so awkward to use that it was discarded. Perhaps a long tube bent in the center to accommodate the angulation of the ducts would work better, but this condition has been successfully treated in another way. The stump of the common hepatic duct is dissected free in the sulcus

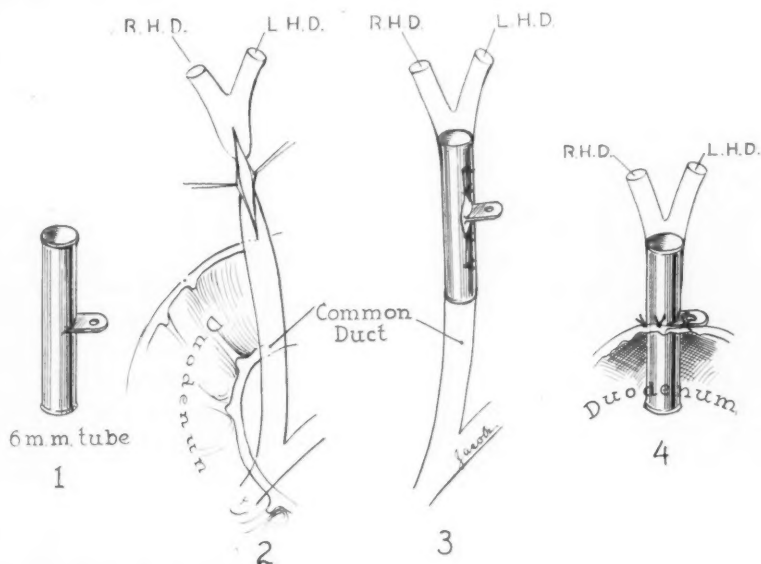


FIG. 2.—(1) The straight tube 3.3 cm. x 6 mm. (2) For holding open a strictured area the duct, the tube is slipped into the duct, which is then closed over it, leaving the anchor flange protruding through the suture line (3). (4) The use of this tube in hepaticoduodenostomy.

transversus of the liver and the common duct is searched for by freeing all tissue off the hepatic artery and portal vein. If it is not found, the duodenum is rolled out and down and the scar tissue beneath it carefully dissected and sectioned. In this way the common duct is usually found underneath the duodenum and so closely attached to it that it appears to be a part of the bowel wall. At this stage the gap may look to be irreparable but after both ends of the duct have been completely mobilized they can be brought together by pushing up on the duodenum and pancreas and pulling on the ends of the duct. End-to-end anastomosis under these circumstances is done under tension, and a stricture will usually form, so this is prevented by doing the anastomosis over a Vitallium tube. Another successful method is to use a rubber T-tube until all infection subsides and after two months reoperate upon the patient, remove the T-tube and insert a Vitallium tube.

COMMON HEPATIC DUCT STRICTURES

The anatomic nomenclature calls the common hepatic duct that part between the bifurcation of the right and left hepatic ducts and the junction of the cystic duct. That below the cystic duct is called the common bile duct. The studies of Nuboer⁶ have shown that because of the anomalies of the cystic duct the common hepatic duct may vary from 0 to 5.8 cm. in length and the common bile duct from 3 to 9.5 cm. in length. Surgeons often speak of the common bile duct as that part which is exposed below the liver in the gastro-hepatic omentum. This is logical, for treatment of this part is the same irrespective of the relation of the cystic duct. On the other hand, injury, or stricture, within 1 cm. of the bifurcation of the hepatic ducts creates distinct problems of management which are not present at a lower level. For the

purpose of this discussion, these will be called common hepatic duct injuries or strictures.

Dr. Howard M. Clute first succeeded in curing a patient with only about one-eighth inch of common hepatic duct remaining after four unsuccessful operations. A Vitallium tube with a trumpet-shaped end (Fig. 3) was designed and inserted into the stump of the common hepatic duct so that it would act as a funnel for the bile from the right and left hepatic ducts. The lower end was placed in the common duct and an anastomosis done over the tube.

Some of the situations encountered in these high strictures of the common hepatic duct are shown in Figure 4. A complete external or internal fistula leading from the common hepatic duct (Fig. 4, No. 1) is usually associated with a closed functionless common duct which must be sought in scar tissue without any tract as a guide to it. The common hepatic duct has been found to empty into a bile-filled cavity (Fig. 4, No. 2) which communicated with an external fistula and



FIG. 3.—The trumpet-shaped tube used by Clute for a high stricture of the common hepatic duct is shown in a postoperative roentgenogram taken with barium filling the stomach.

the common duct. Nature may attempt to reconstruct the injured area by a long, narrow, constricted passage (Fig. 4, No. 3) through scar tissue. This channel may be no bigger than a string and yet carry enough bile to prevent severe jaundice.

Much thought has been given to the design of tubes for use in the hepatic duct strictures. The anterioposterior curvature of the ducts, the bifurcation

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of the hepatic ducts so near the end of the common hepatic duct and the inaccessibility of these structures in the sulcus transversus of the liver create problems in technic that are difficult to overcome. The trumpet-shaped end of the tube (Fig. 4, No. 4) used by Clute does not enter either of the primary

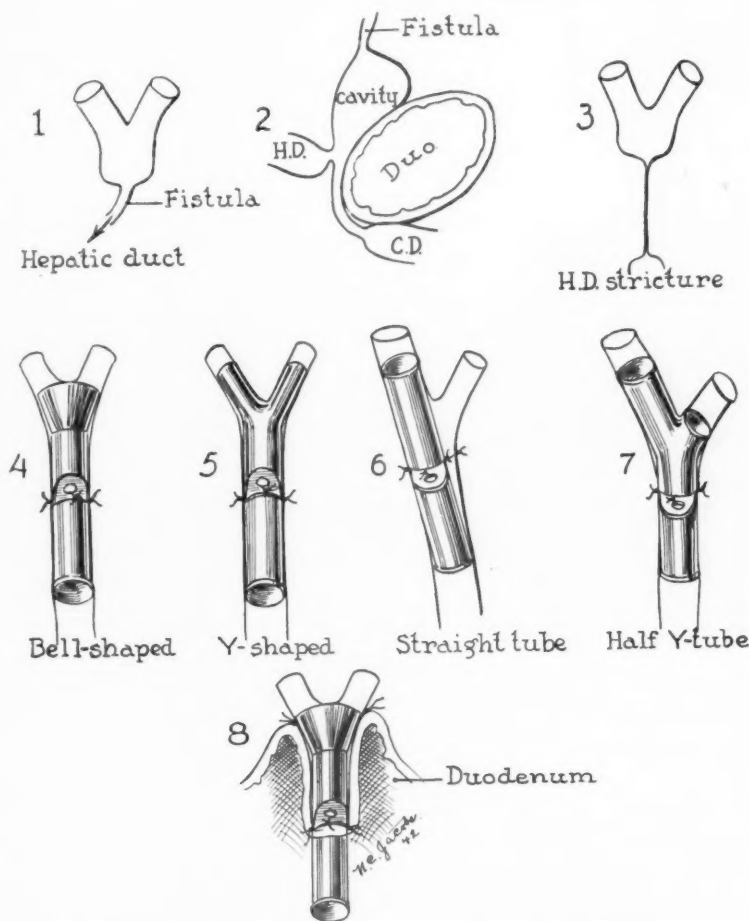


FIG. 4.—The conditions found in strictures of the upper common hepatic duct may include an external fistula (1) associated with a functionless common bile duct, a communication with a bile-filled cavity (2) which drains into a fistula and the common duct or, as in (3) a long thread-like channel joining the ends of the ducts.

In 4, 5, 6, and 7, are illustrated the tubes that have been used in high strictures of the common hepatic duct. Here, the inaccessible bifurcation of the hepatic ducts close to the stricture in a short stump of the common hepatic duct creates mechanical problems of management. Zininger used the bell- or trumpet-shaped tube for hepaticoduodenostomy (8) when the end of the common duct could not be found.

hepatic ducts so has little to hold it in place. If it is unstable and slips away from the hepatic ducts, it may not drain their bile. To overcome this, a Y-shaped tube (Fig. 4, No. 5) was made with 4 Mm. openings at the two proximal ends. Even so, the distance across the two limbs of the Y is 1.3 cm., in contrast to the 1 cm. width of the funnel on the trumpet-shaped tube. The right and left hepatic ducts meet at an angle which varies between 80° and

90°, so the limbs of the Y cannot be brought much closer than this, yet it is difficult to insert them through the stump of the common hepatic duct when they are this far apart. If the hepatic ducts are not too deeply buried in the liver, one or the other can be visualized and slit up the outer side to give room for inserting the Y-tube. In one patient neither the trumpet-shaped nor Y-tube could be inserted so a straight 6 Mm. tube was put up the right hepatic duct (Fig. 4, No. 6) for want of anything better to do. After operation the

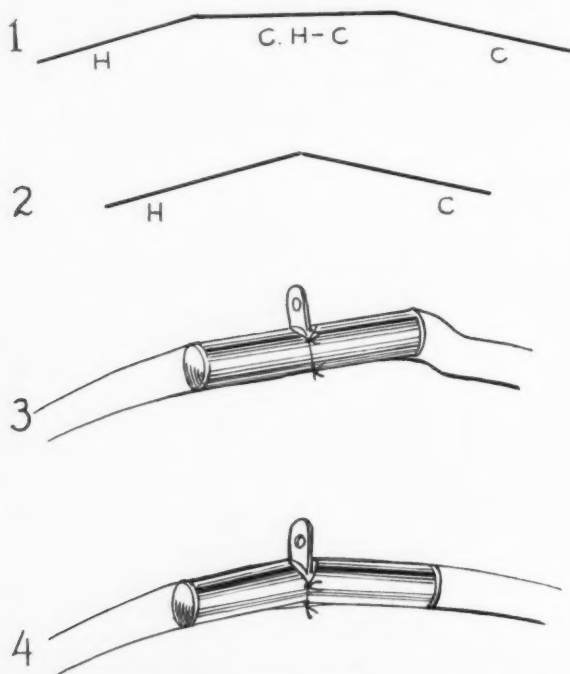


FIG. 5.—(1) The diagrammatic representation of the angulation of the ducts where the hepatic ducts have an anterior inclination, the distal common duct a posterior declination, and the central part of the common hepatic and common bile ducts and horizontal. If this middle part is destroyed (2) then the upper and lower part of the ducts come together at an obtuse angle of about 170°. This causes a straight tube to tip up at one end (3), and may cause pressure necrosis or kinking of the duct. To avoid this a tube has been designed with a bend forming a 170° angle, which will be most useful in the high common-hepatic duct strictures.

left lobe of the liver enlarged, then shrunk and though it may become cirrhotic, yet the patient is well without any signs of hepatic insufficiency. This led to the design of the tube shown in Fig. 4, No. 7, which is essentially a half Y for one limb is cut off. Instead of this, one might have only a hole on the left side so the bile from the left hepatic duct could get into the tube, but unless this opening was accurately placed over the orifice of the duct it would not serve its purpose. Exact placement might be difficult to do by sense of touch so it was thought desirable to have a short stub on the left side to indicate when it was in the correct position. Zininger¹⁰ describes the anastomosis, shown in Fig. 4, No. 8, in a case where no remnant of the common

bile duct could be found. The trumpet-shaped tube was used for hepatico-duodenostomy and this anastomosis secured by rolling the duodenal wall up onto the hepatic ducts.

A straight tube inserted into the hepatic ducts above and the common duct below tends to tilt up at one or the other end. This is due to the slight anterior inclination of the hepatic ducts and the posterior direction of the common duct which is shown in Figure 5. The diagram in Figure 5, No. 1, shows the central part of the common hepatic and common ducts to be horizontal. If this is destroyed so that the proximal hepatic duct is joined to the distal common duct, an obtuse angle is formed. No information could be found in the literature on this,* but measurements taken at operation and on the cadaver showed this angle to be about 170° , or a deviation of 10° from

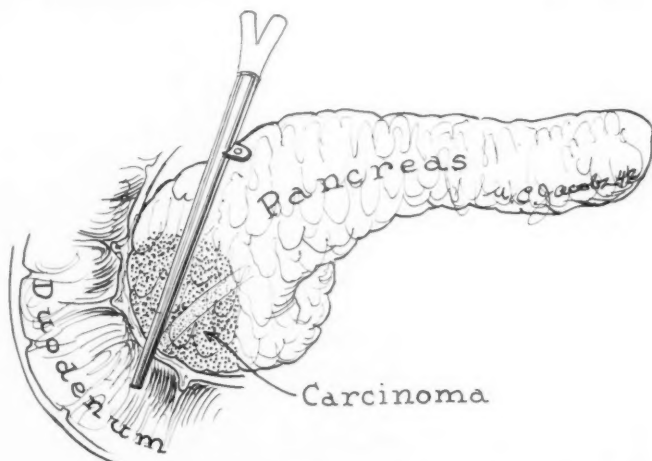


FIG. 6.—An 8 cm. tube which tapers from 6 to 4 mm. in diameter is illustrated. For use in the palliative treatment of occlusion of the bile duct from carcinoma. This might be used instead of cholecystogastrostomy.

the horizontal. To prevent the tilting of the straight tube shown in Figure 5, No. 3, efforts were made to manufacture a curved tube. Vitallium is a very hard alloy which cannot be bent, molded, or machined but must be cast. Curving the tube prevented polishing it around the bend on the inside, so finally the manufacturer suggested welding two pieces of straight tubing together at an angle of 170° , as shown in Figure 5, No. 4. It is expected that all tubes designed for treating strictures of the proximal common hepatic duct will have this anteroposterior angulation. But this raises the question of where to put the bend, for it should come at the site of the anastomosis yet the stump of the common hepatic duct may be as short as 3 or 4 Mm. or as long as 1.5 cm. in different cases. The bifurcation of the hepatic ducts fixes the position of the tube above and the length of the common hepatic duct determines the location of the anchor flange and bend below. A rigid tube cannot be altered to conform to the different distances between these points in different cases so an average length will have to be used. It would appear

*I find that Dr. D. B. Pfeiffer of Philadelphia has described this angulation.

that a length of 1 cm. from the lower part of the bifurcation of the tube to the bend and anchor would meet the needs of most cases.

MALIGNANT STRICTURES

Vitallium tubes have been considered for use in the palliative treatment of malignant occlusion of the bile ducts. The only one that has been made was intended for obstruction from carcinoma of the head of the pancreas. This tube was made 8 cm. long for the average combined length of the common hepatic duct (3.3 cm.) and the common bile duct (6.3 cm.) is 9.6 cm. The tube need not go far up into the common hepatic duct so a length of 8 cm. should permit intubation of the duct into the duodenum. The anchor flange was placed 2 cm. from the upper end where the diameter of the tube is 6 Mm. From this point the tube tapers to 4 Mm. (Fig. 6) to allow insertion through a carcinomatous stricture.

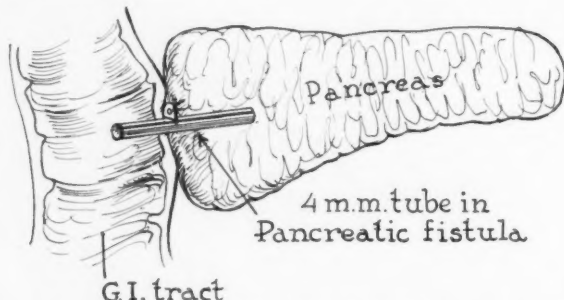


FIG. 7.—A 4 mm.-Vitallium tube is shown inserted into the pancreatic duct for repair of a pancreatic fistula following resection of the head of the pancreas for carcinoma. This method, used successfully by Zinninger, suggests the need of tubes with one short end for implantation into the gastro-intestinal tract.

PANCREATIC FISTULA

A straight Vitallium tube, 4 Mm. in diameter, has been used to close an external pancreatic fistula. The case report sent to me by Zinninger¹⁰ is as follows:

Case Report.—A male, age 62, presented signs, symptoms, and laboratory findings of complete obstructive jaundice from periampullary carcinoma. On October 31, 1939, a first-stage modified Whipple operation was performed. On December 9, 1939, the duodenum and the head of the pancreas were resected for adenocarcinoma of the ampulla of Vater. A pancreatic fistula developed. Every time the fistula closed the patient developed chills and fever, and the fistula had to be reopened. On May 1, 1941, the fistula was traced to the pancreatic stump; one end of the Vitallium tube was inserted into the pancreatic duct (Fig. 7) and the other end implanted into the stomach. The patient's general condition promptly improved. The wound healed by May 19, 1941, and has remained healed ever since.

The use of Vitallium tubes has been thought of in connection with the treatment of some types of hydrocephalus, the repair of ureteral and urethral strictures, and the reconstruction of the vas deferens and fallopian tubes but they have never been reported as used for these purposes.

Discussion.—The question is often asked, what reaction will be caused in the tissues by the presence of Vitallium tubes? Thus far, there is information from only one human case obtained by reoperation, where it was found that little or no reactive inflammation existed. Additional data was sought by means of animal experimentation. Vitallium tubes placed in the common bile duct of dogs remained patent without erosion of the metal or deposition of pigment or salts on them. Most important of all was the absence of reactive change in the mucosa lining of the duct for this would indicate good tolerance of the tissues to the metal. A section of one of these ducts was illustrated in a previous paper.⁷ The mucosa was never found to grow inside the tube so one must depend upon the bare metal for the conduction of the bile. Vitallium is an alloy of cobalt, chromium, and molybdenum which has been found to be inert in bone,^{8, 9} joints,⁴ and the brain^{1, 3} so the absence of reaction in the bile ducts is not surprising.

A review of the various methods of treating injuries or strictures of the bile ducts is not presented, for this audience is already familiar with them and the reviews of Kehr⁵ and Eliot² have discussed them in detail. It is expected that Vitallium tubes will only be used in biliary surgery where extensive damage has occurred and where other methods have failed, for otherwise their indiscriminate use may result in disappointment or even discredit of the method.

SUMMARY

(1) Injury to the bile ducts which was irreparable by other methods has been successfully treated by the permanent implantation of a Vitallium tube.

(2) A straight 3.3 cm. x 6 Mm. tube with a central flange to anchor it in place is most useful to hold open a strictured area of the common bile duct.

(3) Loss of a part of the common duct is best repaired by approximating the ends over a Vitallium tube even if tension must be used. This will hold the ends of the duct together and the tube will prevent occlusion by stricture. It may be dangerous to bridge a gap by tying the tube into the ends of the duct for it may slip out of place.

(4) Injury or stricture of the common hepatic duct within 1 cm. of the bifurcation of the hepatic ducts produces mechanical problems that require special designs to meet them. For this purpose tubes with trumpet-, Y-, and half Y-shaped ends have been made.

(5) Vitallium tubes have been used for the repair of a pancreatic fistula and one has been designed for the palliative intubation of malignant occlusion of the bile ducts. Other uses for these tubes such as in the brain and genitourinary tract have been considered.

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DISCUSSION.—DR. HOWARD M. CLUTE (Boston, Mass.): I think Doctor Pearse's work marks a new step, a new era, if you like, in the management of bile duct strictures, which we all know have been one of the most difficult problems which have faced surgeons, and I think it also is significant because it shows us that in the cavity of the body we may put in this metal and have it stay there for a long time without any material change in the viscus in which it lies. It opens possibilities perhaps for the use of Vitallium in many places in the body other than the common bile duct.

For example, in my hospital the urologist has used a Vitallium tube in the perineal urethra, which constantly strictured following amputation of the penis, and he has been able to have a Vitallium tube fitted into that—which has been used successfully and satisfactorily.

The laryngologist has had a mold made to use in the stricture of the larynx, which he was trying to treat with skin grafts, and hopes to overcome the stricture.

My personal experience with Vitallium tubes is limited to a case conducted by my associate, Doctor Albright, about two weeks ago, in which I helped.

There is another case of a friend of mine that I advised, Doctor Hedisheimer, of New Bedford. Doctor Hedisheimer's case has gone on for some five months now. Doctor Albright's is very recent.

Then there is the other case that Doctor Pearse mentioned, the case I cared for myself. I would like to show the lantern slides of that, if I may. This lady had had four previous operations, starting with her original cholecystectomy and injury to the common duct, and three other operations to repair this, two of which I had performed, the fourth operation, the last one that I did being a cholecystohepaticoduodenostomy. In six or eight months this failed to function any further, and we finally reoperated upon her for the fifth time, after learning from Doctor Pearse of these tubes.

This is more or less the picture that we found after we had separated the duodenum from the common duct. We found complete absence of the common duct in this area. The picture does not show it but we catheterized the common duct through the ampulla of Vater, and that helped in finding this at the distal end, which by no means is as clear as the artist has drawn.

The tube we used was a funnel-shaped affair which we had made, because we knew, from three previous excursions into this area, that this stricture was deeply into the liver and we would have a very difficult time to hold anything in it. The funnel-shaped tube was then put in the liver, the other end over here. The surrounding tissue was laid around it as well as we could. Silk sutures were put here in this very dense fiber that remained in the common hepatic duct. I think it was good fortune that in the 16 months past, since this operation the tube has not slipped out. However, it is to be noted, it seems to me, that in this case we had a gap larger than the artist shows, in my recollection three-quarters of an inch, in which there was no common bile duct at all. If the gap had not been here, I agree with Doctor Pearse that it would have been very much to our advantage to approximate the ends, and this no doubt could have been done if one freed the duodenum and freed the hepatic duct.

This is a slide similar to the one Doctor Pearse showed you, but taken some six months after the operation, when the patient had an attack of pain and a slight jaundice.

and I was afraid that something had happened, but it cleared up in a matter of two days. We took this picture just to see whether the tube was where it should be, and it was.

The last slide shows the various tubes I got from Doctor Pearse and some we had, for your observation of the types that have been made. Doctor Pearse has enlarged on these since then. Though it is apparent that this tube can be used to replace absent common duct and that it will last for a long time, and I believe from this case at least that you can have the common duct absent over quite a distance and not pull the two ends of the duct together, as Doctor Pearse recommends and as we recommend, and still have it go on, there is more danger, of course, that the tube may fall out.

I think there is a great advantage, and it is to be emphasized, that you should have the distal end of the common duct toward the distal end of the tube if possible, as Doctor Pearse has said, because in that way you preserve the sphincter of Oddi, and which is of great advantage. In fact, I think it is of such advantage that in Doctor Albright's case I could not find the distal duct and urged him to open the duodenum and find it from within, and having opened the duodenum we found it.

It seems to me that these tubes can be used in biliary strictures of certain kinds. Certainly, I believe they have an advantage over any such procedure as transplantation of external biliary fistula, which carries such a high percentage of failures. I think they are preferable to rubber tubes, even with the slight knowledge we have, and are very valuable when one can use them with the preservation of the sphincter of Oddi, as in these instances.

DR. EUGENE W. ROCKEY (Portland, Ore.): Not knowing of Doctor Pearse's work, some three years ago, I attempted a somewhat similar series of experiments on dogs, using several different substances, and finally settled on metallic magnesium. I found that with those dogs there was no irritation of the gallbladder wall when the tube was implanted into it, and that I got the tubes of the thickness so that they would last from eight to 12 weeks. There was no bile deposited in these tubes.

I then implanted such tubes in two humans. The tube did not have the advantage of the lateral flange which Doctor Pearse had, and in one case the tube slipped down into the duodenum. That was an implantation in the duodenum.

I was about to publish this experience and got a new lot of metallic magnesium tubes from the Dow Chemical Company. I planted those in the dogs' gallbladders and had the misfortune to find that bile salts were deposited on the tubes, which had not been the case originally. I sent the magnesium back to have it analyzed and find whether it was pure magnesium or had some alloy in it which was irritating.

The Vitallium tube apparently has a distinct advantage over the metallic magnesium which I have been using, but I am sure there is a very great need for such a bridge for a stricture of the biliary duct.

DR. WALTER G. MADDOCK (Ann Arbor, Mich.): About a year ago, I first heard of Doctor Pearse's work with the use of this tube, and he supplied two for us to use. I have had the opportunity of trying them on two patients.

The first one, about 11 months ago, came in with a history of multiple previous operations for obstruction to the common duct. This patient had a T-tube in place, and I simply took the T-tube out and slipped the Vitallium tube into the site of it, and it seemed to fit nicely in that direction and did not move up and down. This patient has gone ten months without any difficulty as far as the obstruction is concerned. During the past month, however, she has begun to have attacks of chills and fever and jaundice. It may be that she will get over it, as Doctor Clute's case did, but I am much concerned about the situation, and I feel that something subsequent may be necessary.

A month ago I had a chance to use the tube again on a much similar case, with previous history of operations upon the common duct because of stricture occurring post-operatively. At this time a rubber T-tube was in place. The common duct was cleared downward, but the approach to the hepatic ducts was not as wide-open as I would have liked it. I could not get a uterine sound up that section very well. A small probe, however, did pass. The patient had requested, however, to dispense with the rubber tube, if possible, so I slipped one of these Vitallium tubes into place with-

out disturbing the site of it very much. That patient has not done well. She is having chills and fever, and has had intermittent jaundice on two occasions.

I think this is just an addition to the experience with these Vitallium tubes, and fear that my two cases are going to require some further type of treatment. I do not know what it is going to be.

DR. LEO ELOESSER (San Francisco, Calif.): Just two short points of technic. In a man who had had a very complicated history, including fistula between his transverse colon and his gallbladder, a bleeding duodenal ulcer, and several other complications, an obstructive biliary cirrhosis ensued, with an intermittent obstruction, sometimes on his right and sometimes on his left. In the first attempt to overcome this obstruction, finding a very tight duodenum and having had a bleeding ulcer to deal with, we did a hepaticoduodenostomy and anastomosed the open stump of the duodenum to the hepatic junction. That gave a very wide union between the hepatic junction and duodenum, but the wide union still was not sufficient to overcome the strictures which reformed in the hepatic duct.

I used one of Doctor Pearse's tubes and slipped it into the right duct, but I was confronted with the same situation that he delineated on the second line of his third slide. I think, the last one to the left, in which there was a little button projecting, as it were, as a flange from the side of the tube, because the situation of the duct was such that it would have been quite impossible to introduce a Y-shaped tube. I questioned in that case whether it would be feasible, although I had none at hand, to make a tube with a clip joint, as it were, so that it would be possible to introduce one branch of the Y and then snap the other branch Y into the other hand of the hepatic ducts.

The patient, to whom I refer, died five days after his operation of secondary rupture of his wound and pneumonia. We obtained the specimen, and the tube was in place. There was no effect of the tube on the surrounding tissues and no erosion, and the tissues were perfect in reaction.

DR. HERMAN E. PEARSE (closing): One word about bridging the gap. We have attempted to do this by a longer tube, long enough to prevent the ducts retracting off. The disadvantage was the tilting of the tube, and when a straight tube, 6 cm. long, was made, it was too awkward to be of any use. Now that we have a method of making an angulated tube, it may be possible to devise one long enough to bridge an extensive gap.

I was very much interested in Doctor Rockey's comments, because I am at present contemplating some experiments with Dow metal for an entirely different purpose. Men who have been wounded in aircraft combat, who had fragments of magnesium in their tissues, have been found to develop an extreme fibroplasia about metallic magnesium, so much so that Doctor Walters has been able, experimentally, to shut off the ureter by encircling it with a clip of Dow metal. I was interested in this as another possible means of gradually occluding large arteries by fibroplasia.

It is interesting that magnesium in the biliary system did not produce this fibroplastic reaction.

Of the two patients mentioned by Doctor Maddock, the latter one might well be reoperated upon, perhaps, with the insertion of a tube above the hepatic stricture. We have had one instance of recurrent chills, fever, and jaundice in a patient one year after intubation, in which we suspected occlusion of the tube from cholesterol. We gave her sodium taurocholate and these symptoms disappeared.

Also, one must remember that these patients have had a long history of liver infection and some of their postoperative difficulty may be due to hepatitis.

SPONTANEOUS INTERNAL BILIARY FISTULA*

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FISTULAE between some portion of the biliary tract and some hollow viscus have been known to exist for many years. Pathologists have described fistulous communications between the gallbladder or bile ducts and nearly all portions of the gastro-intestinal tract as well as with the bladder, uterus, kidney pelvis, portal vein, ovarian cysts, and with such intrathoracic structures as the pericardium and bronchial tree. In an excellent literature review and survey of their own material, Borman and Rigler record the presence of only 67 internal biliary fistulae in over 30,000 autopsies. Many such passages undoubtedly were overlooked because intestinal obstruction due to gallstones was mentioned in the early literature three times as frequently as gallbladder intestinal fistula.⁴ Undoubtedly most gallstones sufficiently large to produce obstruction have reached the lumen of the bowel through a fistula.

With the more frequent recognition of internal biliary fistulae in the operating room and their frequent roentgenologic diagnosis, clinical interest in this condition has increased. Kehr reported the finding of 100 biliary fistulae in 2,000 cholecystectomies, an incidence of 5 per cent. Bernhard encountered them 109 times in 6,263 operations upon the biliary tract. At the University Hospitals of Iowa 1.2 per cent of all patients with cholecystitis were found to have internal biliary fistulae.⁵ Judd and Burden reported 153 fistulous connections between the biliary and gastro-intestinal tracts. The great majority of these were not diagnosed before operation. In Judd and Burden's series only two were diagnosed preoperatively, one of which was visualized roentgenographically.

Roentgenographic diagnosis of internal biliary fistula is based chiefly upon the presence of air in the biliary passages or the influx of barium during a gastro-intestinal study. The passage of barium was noted first by Hunt and Herbst in 1915. During the following ten years many reports have been made of roentgenographic recognition of internal biliary fistulae. Borman and Rigler collected all reports to 1937 which totaled as follows:

Cholecystoduodenal.....	31
Choledochoduodenal.....	16
Cholecystocolic.....	10
Cholecystogastric.....	3
Cholecystoduodenocolic.....	1
Cholecystojejunal.....	1
Choledochocolic.....	1
Biliary-bronchial.....	4

They also listed 16 instances of regurgitation of barium into the common duct. In spite of the increased interest in and recognition of such fistulae by

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roentgenologists, it is probable that only a small percentage of them are diagnosed prior to operation. This is due largely to the small numbers of such patients upon whom gastro-intestinal roentgenologic studies are made.

Most internal biliary fistulae are formed by the erosion of a gallstone through the wall of the gallbladder or common duct into an adjacent viscus. Obstruction of the ducts below the stone is usual and a severe inflammation is thought to accompany the process. Duodenal ulcers are believed occasionally to invade the adjacent wall of the gallbladder and produce a fistula. Malignant lesions also are considered as etiologic factors.

In a series of 500 operations for benign biliary tract diseases I have encountered spontaneous internal biliary fistulae in 16 patients, distributed as follows:

Cholecystoduodenal.....	9
Cholecystoduodenal and cholecystocolic.....	1
Cholecystocolic.....	2
Cholecystogastric.....	1
Cholecystocholedochal.....	1
Hepaticoduodenal.....	1
Hepatobronchial.....	1

SYMPTOMATOLOGY

It frequently is stated that patients who develop spontaneous internal biliary fistulae give a very longstanding history of gallbladder disease, often severe, with colics, fever, and jaundice, and then after a particularly severe attack are relieved of all of their symptoms. It is thought that the formation of the fistula is followed by a relief of distress. Such has not been true in this series.

The duration of symptoms varied from one month to 27 years. Four patients had symptoms for less than one year and four others for less than four years. The average duration of symptoms for the group was eight years in comparison to six years for the entire group of patients with biliary disease. Moderately severe to intense colics were complained of by all patients. All but four patients complained of fever, usually accompanied by chills. Recurrent or fluctuating but persistent jaundice occurred in 11 of the 15 patients with intra-abdominal fistula. The majority of these patients were acutely ill, debilitated, and many lost from 20 to as much as 80 pounds in weight. In no case was intestinal obstruction present due to stone but one patient had marked duodenal obstruction due to pressure of the distended gallbladder and cicatricial stenosis at the site of a cholecystoduodenal fistula. The majority of these patients were much sicker and had more severe symptoms than usually are seen in cholecystic disease. In most instances there was a steady progression of symptoms and in none was the history suggestive of relief of symptoms coincident with the formation of an internal fistula.

In this group of 16 patients, preoperative roentgenographic diagnoses were made in two cases. In one with a cholecystoduodenal fistula the gallbladder filled with barium (Fig. 1) during a gastro-intestinal study. Several days later many of the intrahepatic bile ducts had become filled with gas and

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were outlined on roentgenograms (Fig. 2). A barium meal administered to the other patient revealed a cholecystogastric fistula. This case is discussed later in detail. Two other patients at the Illinois Research and Educational Hospitals have had roentgenographic diagnoses of internal biliary fistulae; one patient whose roentgenograms revealed a cholecystoduodenal

FIG. 1.



FIG. 2.



FIG. 3.

FIG. 1.—Cholecystoduodenal fistula. Gallbladder filled with barium.

FIG. 2.—Same patient as Figure 1. Film taken some time later revealing gas throughout gallbladder and bile ducts.

FIG. 3.—Regurgitation of barium through choledochoduodenal fistula visualizing bile ducts, gallbladder, and one large stone in the choledochus.

fistula refused to be operated upon. Roentgenograms of the other patient revealed a choledochoduodenal fistula (Fig. 3). She was operated upon by Doctor Warren H. Cole, who found an opening between the common duct and the superior margin of the duodenum, evidently produced by the erosion and passage of a stone. Other stones were found in the common duct.

OPERATIVE FINDINGS AND PROCEDURES

Seven of the nine patients with cholecystoduodenal fistulae gave a history of jaundice. All seven had one or more large stones present in the common duct. One of the two patients without a history of jaundice had an obliterated cystic duct. The fistula into the gallbladder was large and patent and the

gallbladder was badly diseased. The common duct was not enlarged or diseased and did not contain stones. Evidently this patient developed a cystic duct obstruction before the fistula was formed and the bile ducts were not subjected to contamination by regurgitated intestinal contents. The other patient without a history of jaundice had been operated upon 18 years previously and was of the opinion that her gallbladder had been removed. After frequent attacks of epigastric pain for many years she finally developed symptoms of duodenal obstruction. A diagnosis of an obstructing duodenal ulcer was made. At operation the gallbladder was present and filled with stones. The cystic duct was very small and the common duct appeared normal. A patent fistula existed between the gallbladder and duodenum with marked stenosis of the intestine. Cholecystectomy was performed and the duodenum closed but as the lumen of the bowel was very small, a posterior gastro-enterostomy was made.

One male patient, aged 42, gave a history of biliary colics with jaundice for 17 years. Four years before coming under our care a cholecystostomy had been performed. Attacks of pain, fever, and jaundice occurred a few days after operation and recurred at frequent intervals. He became progressively more emaciated and more frequently jaundiced. For six weeks prior to our first operation he had constant chills, fever, and jaundice. A patent cholecystoduodenal fistula was taken down and the duodenum closed. Extensive edema and infection were present throughout the entire extrahepatic biliary tract. The common duct was greatly dilated, thickened, and contained "white bile," many large and small stones with much sand and pus. The gallbladder was filled with stones and was removed. The common duct was emptied and drained with a T-tube. The patient recovered and was well for six months when he again developed colics and jaundice. The common duct was reexplored and found to be filled with stones. These evidently had formed since the last operation. The inflammatory changes in the ducts noted at the previous operation had greatly subsided. All stones found were removed and the duct again drained for a month. The patient remained well for six years when he again had mild attacks of biliary colic with transitory jaundice but without fever. A third exploration of the common duct revealed one stone at the distal end. All evidence of infection in the duct wall had disappeared. He has been free of symptoms since this operation.

The patient with both cholecystoduodenal and cholecystocolic fistulae had been jaundiced. After dividing the fistulae and closing the stomata in the colon and duodenum, exploration revealed marked infection of the gallbladder with edema and inflammation throughout the gastrohepatic omentum and inflammatory lymphadenitis. Because of this, only a partial cholecystectomy was performed and the common duct was not explored.

Both patients with cholecystocolic fistulae had persistent right upper abdominal pain and tenderness associated with fever for several weeks. Neither had been jaundiced. At operation one patient had an extensive inflammatory mass and in attempting to isolate the gallbladder a large cholecystocolic fistula

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was separated. The large opening in an acutely inflamed hepatic flexure of the colon was closed with difficulty. The gallbladder was removed but the common duct was not exposed because of the extensive edema and inflammation. The second patient likewise had marked swelling and acute inflammation of the gallbladder and bile ducts. After taking down the fistula and closing

FIG. 4.



FIG. 5.

FIG. 4.—Barium has passed through a cholecystogastric fistula outlining gallbladder and both extra- and intrahepatic bile ducts. Calculi can be seen displacing barium in gallbladder and in the distal end of the choledochus.

FIG. 5.—Film taken 24 hours after Figure 4. Considerable barium is still present in the intrahepatic ducts.

FIG. 6.—Same as Figure 4. Film taken six days after administration of barium showing that most of the barium had passed out of the liver through the fistula.

FIG. 6.



the colon, it was thought safer to remove only a portion of the gallbladder. The virulence and acuteness of infection in the gallbladder and bile ducts was much more marked when cholecystocolic fistulae existed than when the gallbladder communicated with the duodenum.

Cholecystogastric fistulae are much less frequently found than cholecystoduodenal stomata because of the less frequent anatomical proximity. Three

previous cases have been diagnosed by roentgenograms.³ Because of a number of interesting features of our case, a brief abstract of the history is given:

CASE REPORTS

Case 1.—R., male, age 62, had no symptoms referable to the gastro-intestinal tract until six months prior to the time of operation. During this time he complained of qualitative food distress manifested by bloating and belching. Two weeks before admission to the hospital he noted midepigastria distress and the onset of a gradually increasing jaundice. A week later he had his first chill with a fever of 102° F. Upon admission to the hospital a barium meal revealed a cholecystogastric fistula and visualized the intrahepatic bile ducts (Figs. 4, 5 and 6). A stone could also be seen blocking the lower end of the choledochus. For three weeks chills and fever recurred almost daily. The passage of barium into and out of the liver and the presence of bile in the duodenal contents indicated that the fistula was patent. The icterus index remained at 60. At this stage the patient evidently was suffering from a severe cholangitis and hepatitis induced by the reflux of intestinal contents into the bile ducts and his jaundice was intrahepatic in type (Chart 1).

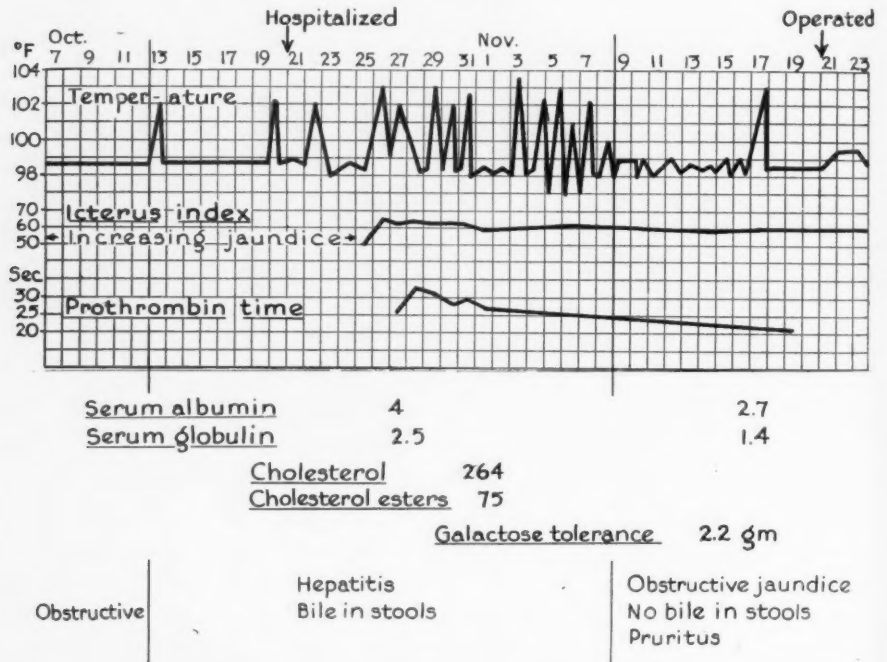


CHART 1.—Showing temperature throughout various phases of illness. The level of icterus index and other laboratory studies are shown. Periods in which the jaundice was thought to be of intrahepatic and of extrahepatic origin are indicated.

His condition gradually improved, the fever subsided and he appeared less toxic. However, following the subsidence of fever, bile disappeared from the duodenal contents and did not return. The icterus index remained at 60, jaundice evidently persisting at this level because of obstruction to the extrahepatic ducts. Pruritus developed. Although low serum protein levels and a high return of galactose in the urine indicated considerable liver damage, the patient appeared improved clinically and as total obstruction to the bile ducts now existed, surgery seemed indicated.

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At operation a fistula was found between the fundus of the gallbladder and the prepyloric portion of the anterior wall of the stomach. The lumen was almost obliterated. The gallbladder contained a number of calculi and one large stone was found in the distal end of the common duct evidently causing complete obstruction. The fistulous opening into the stomach was closed, the stone removed from the choledochus, and the gallbladder removed. Recovery was satisfactory but slow, the patient being dismissed on his nineteenth postoperative day. The jaundice did not entirely disappear for two months.

This patient presents an interesting sequence of events. The onset of jaundice evidently was due to the stone blocking the common duct and was purely obstructive in nature. Distention and inflammation of the gallbladder was followed by the establishment of a cholecystogastric fistula. Although this permitted free drainage of bile into the gastro-intestinal tract, regurgitation of intestinal contents into the bile ducts produced a severe cholangitis and hepatitis lasting three weeks. During this period the degree of jaundice remained constant but was due to hepatitis rather than to obstruction. The presence of bile in the stomach confirmed the patency of the fistula. I believe surgery at this time would have been extremely hazardous as no obstruction existed and the liver was acutely diseased.

After the chills and fever subsided, the fistula evidently closed and again his jaundice was on an obstructive basis. This was suggested by the subsidence of fever, the absence of bile in the stomach, the persistence of jaundice at the same level, and the development of pruritis. In spite of laboratory evidence of diminished hepatic function, the patient was clinically improved and surgery now seemed imperative to relieve the obstruction.

Fistulae between two portions of the extrahepatic biliary tract are rare. The one case in this series gave a four months' history with several attacks of severe right upper abdominal pain followed by chills, fever, and jaundice. At operation the cystic duct was found to be very small. A large fistulous opening formed a second communication between the ampulla of the gallbladder and the dilated and thickened choledochus. One large stone was removed from the distal end of the common duct and the gallbladder was completely excised.

The fistula existing between the common hepatic duct and the duodenum developed spontaneously, following damage to the choledochus during cholecystectomy. Biliary colics had occurred for several years prior to cholecystectomy but fever and jaundice were absent. Following operation jaundice developed and persisted almost constantly though varying greatly in intensity. One year later this patient came under our care, moderately jaundiced but with bile present in the duodenal contents. At operation a stricture of the common duct was found with a fistulous tract extending from the common hepatic duct to the duodenum. This was excised, the duodenal opening closed and a plastic repair of the common duct performed.

Fistulae originating at the liver or bile ducts and extending through the right diaphragm to communicate with a bronchus usually are due to gallstones, to amebic abscesses, or to hydatid cysts of the liver. There is often a preceding

history of biliary disease with evidence of an elevated right diaphragm and later pleural effusion. Bile in the sputum is the most diagnostic finding. The following case is of interest because the hepatobronchial fistula was secondary to streptococci abscesses of the liver and the patient recovered.

Case 2.—A previously healthy, 26-year-old, white, male, developed general malaise, headache, and fever. After being treated for influenza for a week he did not improve and was hospitalized. His temperature ranged between 101° F. and 104° F. The liver edge extended progressively lower and the right diaphragm steadily became elevated. Liver abscess was suspected but no improvement followed the administration of sulfanilamide or emetine. A right-sided pleural effusion was noted and gradually increased. This was soon followed by jaundice, shooting pains in the right upper quadrant, and tenderness over the liver. The appearance of bile in the sputum established the diagnosis of an hepatobronchial fistula. Three weeks after the onset of symptoms, an abscess high in the dome of the liver was drained through an anterior subcostal incision. This approach was used because it overlay the area of greatest liver tenderness. Nonhemolytic streptococcus was found in the abscess contents. Improvement followed this operation, bile disappeared from the sputum but drained freely from the wound and his fever subsided. One month after operation he again became febrile, bile returned to the sputum and abdominal pain recurred.

A second operation was performed, the twelfth right rib being resected and the subphrenic space entered posteriorly. In approximately the middle of the dome of the liver an abscess was found adherent to the diaphragm. The liver was separated from the diaphragm and a large cavity filled with necrotic tissue and pus was located in the dome of the liver. Again nonhemolytic streptococcus was found. Bile soon disappeared from the sputum. Drainage persisted both anteriorly and posteriorly for many weeks. The patient slowly improved and was discharged from the hospital three months after operation.

RESULTS

The mortality of surgery for internal biliary fistulae, generally, is considered to be much greater than for uncomplicated biliary tract disease and has been reported at 10 per cent or higher. In this series of 16 patients there were three hospital deaths, a mortality of nearly 19 per cent. This is very high when compared to our mortality of 1.2 per cent for uncomplicated cholecystectomies. Although two deaths, one patient with a cholecystoduodenal fistula, the other with a cholecystocolic fistula, were attributed to cardiac failure on postmortem examination, it is evident that the debility, liver damage, and prolonged sepsis associated with the internal biliary fistulae were largely responsible for failure of recovery. The third death occurred in the patient with a cholecystoduodenal fistula with associated duodenal obstruction. This patient's symptoms suggested gallbladder disease but as she firmly believed that her gallbladder previously had been removed, she refused surgery until duodenal obstruction was nearly complete and had resulted in marked emaciation and nutritional deficiency.

The morbidity of biliary surgery complicated by internal fistulae likewise is increased. The average length of hospital stay after operation was 23.5 days compared to 12.7 days for all other operations for benign biliary tract disease. The time required for the disappearance of jaundice, return of weight and strength, and ability to return to normal activities was several times that following surgery for uncomplicated biliary disease.

DISCUSSION

It has been stated that the development of a spontaneous internal biliary fistula is nature's cure of an obstruction to the bile ducts. That "the cure is worse than the disease" is well substantiated by the increased mortality of biliary tract surgery when fistulae exist. In this series of cases, the relief of symptoms which is claimed to follow the establishment of a new opening between the gallbladder and gastro-intestinal tract did not occur. Almost invariably the patients became progressively worse. Chills, fever, and leukocytosis indicated a severe inflammatory disease. Gradual weight loss and weakness indicated a disturbance of nutrition possibly on the basis of a damaged liver. Jaundice in the absence of obstruction was a very frequent finding and indicated cholangitis and hepatitis. As these symptoms are far more frequent and severe in the presence of fistulae than in other cholecystic disease, it is evident that the regurgitation of intestinal contents into the bile ducts is very damaging to them and to the liver. This is true whether the contamination be from the stomach, duodenum, or colon. However, colon contents seem to produce a more acute and virulent reaction. The chemical action of gastric or duodenal secretions may be a factor.

The distal end of the choledochus is provided with three important structures to prevent duodenal regurgitation. The sphincter of Oddi, although serving largely to regulate the flow of bile into the duodenum, may act as a barrier. The oblique course of the choledochus through the musculature of the duodenum utilizes the action of these muscles to compress the duct when tension in the duodenum is increased by peristaltic contraction. Most important, however, are the valve-like folds lining the ampulla of Vater which permit bile to flow out but very effectively prevent duodenal regurgitation. This can be demonstrated experimentally by greatly increasing intraduodenal pressure without forcing contents into the common duct. It is demonstrated clinically by the infrequency with which barium is noted to pass into the bile ducts during gastro-intestinal studies. When such regurgitation does occur, there is usually some pathological change in the distal common duct. Most often this consists of a fibrosis and destruction of the valves in the ampulla of Vater resulting from the passage of a large gallstone into the duodenum. Such protection against the entrance of intestinal contents into the bile ducts would hardly be warranted if these contents were harmless.

The experimental work of Beaver, and others, has shown that in animals, when free communication between the gastro-intestinal tract and bile ducts is established by cholecystogastro-intestinal anastomoses, progressive liver damage occurs. Liver damage has likewise been apparent in this series of patients with internal biliary fistulae, and has been demonstrated not only by liver function tests but also by the prolonged period of time elapsing after operation before jaundice entirely disappears.

The preoperative diagnosis of internal biliary fistula is being made more often with frequent and more thorough roentgenologic studies. Clinically the

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DISCUSSION.—DR. HUGH H. TROUT (Roanoke, Va.): I would like to report a case of intestinal obstruction due to a gallstone, and the roentgenographic findings in the common duct. Incidentally, we did not make this diagnosis before the gallstone was removed. In taking a plain roentgenogram of an intestinal obstruction case, we were very much surprised to find the common duct greatly dilated with air. I do not know how many of you have seen intestinal obstructions due to large gallstones, but I think you will find that is fairly common. The gallstone passes through the common duct, obstructs the duodenum, and as the gas backs up the common duct is also dilated. If you want to make a diagnosis of intestinal obstruction due to gallstones, this may help you.

DR. JOHN M. FINNEY, JR. (Baltimore, Md.): Doctor Puestow said something about hesitating to speak about such minor surgery as internal biliary fistulae after the program which has preceded this paper. From my experience this is not in the minor surgical class.

I want to cite two instances which I think are rather interesting, particularly the second one, exhibiting complications which one may encounter with this type of case.

The first case that I cite is one we saw a good many years ago, in which there were multiple biliary fistulae. I do not think that this was entirely due to the surgical handling. But when the gallbladder was finally isolated, it was found that there was a fistula medially between the gallbladder and the stomach, posteriorly between the gallbladder and the duodenum, and inferiorly between the gallbladder and the transverse colon.

The other case was one in which I was called to see suffering from profuse intestinal hemorrhage, rather fresh, and the patient was in bad condition. The only history, to which we did not attach any particular importance at the time, was that of a prolonged illness of about three months' duration, 12 years previously, with pain in the right upper quadrant, and considerable wasting during that period of time. We thought that the hemorrhage was possibly coming from a bleeding ulcer in a Meckel's diverticulum, because, while the blood was partially changed, it came through fairly bright.

The interesting finding, which we did not interpret before operation, was a large calcified shadow about the size of a good-sized orange in the region of the right lobe of the liver, which we considered to be a calcified cyst of some sort.

With considerable difficulty, and many transfusions, the patient was prepared for operation, at which time we found that the calcified body was a completely calcified gallbladder, which had become adherent to, and perforated into, probably 12 years previously, the transverse colon, and that a calcified piece had broken loose from the inside of this calcified gallbladder and had tried to pass through the fistula, which was about 0.5 cm. in diameter. In so doing had severed a large vessel in the mesenteric margin of the transverse colon.

This patient did not do very well, and developed numerous fistulae. He was readmitted to the hospital about five months later, where he died, eight months after the original operation, of actinomycosis of the lung, the chest wall, the abdominal wall, and liver, presumably all of which was acquired at the time of the separation of the original fistula between the transverse colon and the gallbladder.

DR. JOHN A. WOLFER (Chicago, Ill.): Doctor Puestow mentioned the matter of weight-loss, also the prior history. It reminded me of a patient I saw some years ago who, so far as we could determine, had no prior history of any acute intra-abdominal catastrophe. He was seen at the hospital, a diagnosis having been made of carcinoma of the hepatic flexure of the colon. This was made upon a history of a weight-loss of 40 pounds, relatively rapidly, and a defect shown by barium enema.

condition should be considered in patients with biliary colics accompanied by chills, fever, and jaundice, especially when these symptoms are frequent, persistent, and progressive. Frequent determinations of the presence and amount of bile in the duodenum is important both diagnostically and in determining the advisability and time of surgery. A persistent jaundice associated with a wide open biliary fistula which permits bile to flow from the bile ducts indicates that hepatitis exists and should make one cautious in instituting surgical therapy. As both the mortality and morbidity of surgery for internal fistulae are very high, good judgment and intensive preoperative care are essential. Likewise, the postoperative course is apt to be stormy and great care must be taken to protect the liver.

The calculi present in the choledochus of most of our patients found to have choledocholithiasis were formed in the gallbladder and passed through the cystic duct. Only a small percentage of these patients gave a history of persistent chills and fever and at operation acute cholangitis rarely was found. I believe that stones seldom form in the common duct in the absence of infection. However, when acute cholangitis exists, as is so frequently seen in internal biliary fistulae, stones may reform repeatedly in the bile ducts. This was demonstrated in the patient with a cholecystoduodenal fistula and severe cholangitis and hepatitis who had three common duct explorations for the removal of reformed stones.

SUMMARY

A series of 16 spontaneous internal biliary fistulae are presented. In evaluating the histories, pain, chills, fever, and jaundice generally were present. These patients did not obtain apparent relief of symptoms with the spontaneous establishment of a fistula, but became progressively worse.

At operation, stones were found obstructing the common duct in a majority of cases. Cystic duct obstructions were present in two.

Severe inflammation of the extrahepatic biliary system was present in most instances. This evidently resulted from contamination by intestinal contents. Liver damage of varying degrees likewise was associated.

Jaundice is a usual accompaniment of internal biliary fistulae and one must determine whether this is due largely to obstruction or to hepatitis. The degree of drainage of bile by the fistula as indicated by the amount of bile in the intestine is an important guide.

Stones may reform in the bile ducts in severe cholangitis.

Hepatic damage usually accompanies internal biliary fistulae and necessitates careful judgment as to the time of operation and intensive pre- and postoperative care.

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Upon operation, there was found a granuloma-like mass involving the fundus of the gallbladder and hepatic flexure of the colon. The gallbladder was removed, the colon defect repaired, and strangely, following this operation he gained his weight just as rapidly as he had lost it. In the matter of two or three weeks he had gained back half his weight-loss and went on to uneventful recovery.

I was wondering whether one of two things might obtain; whether he lost weight by virtue of bile probably passing into the colon, so that it was not made available for use, or if he had an ascending infection which may have produced a varying degree of hepatitis which accounted for his weight-loss. I do not know yet as to which of these factors might have obtained. To me it was unusual, and I was interested to hear Doctor Puestow say he had seen so many cases, because, when everything is said and done, I do not believe they are so common, and I am certainly glad they are not.

DR. J. DEWEY BISGARD (Omaha, Nebr.): About a year ago I explored a case upon a diagnosis of a choledochoduodenal fistula, and found that I was in error. This is the film upon which the diagnosis (slide) was made, showing barium entering the common bile duct, which persisted after the stomach was emptied of barium, at the end of six hours. It also showed, in looking over the film subsequently, this filling and some dilatation in the duodenum. This patient had about an eight months' history of digestive disturbances, which I will not go into, and had had a cholecystotomy, so had a background for this picture.

(Slide) At exploratory operation, a primary lymphosarcoma of the duodenum was found, and this is the specimen which I resected by a one-stage Whipple operation. This shows the cause, of the barium, showing in the common bile duct. You see the wooden rod there, passed through the distal end of the common bile duct and coming out in the center of this tumor, and, either as a result of destruction of the ampulla or as a retraction from the tumor it has become incompetent and permitted the barium to enter the common bile duct.

I am showing this both as a possible error in interpretation of the roentgenograms, and also as an example of another indication for the Whipple operation.

(Slide) That is the other slide, showing the common duct in the upper part.

DR. CHARLES B. PUESTOW (closing): The cases that have been presented are very interesting and I would like to make one comment. Three years ago next month, while attending the meeting of the Swedish Surgical Society, a paper was read in which the recommendation was made to perform a cholecystogastrostomy or cholecystoduodenostomy for common duct stones, feeling that that was a safer procedure than to go down and explore the common duct. In view of what happens to the bile ducts and to the liver, it seems to me that that procedure would be rather hazardous for the patient.

REFLEXES ORIGINATING IN THE COMMON DUCT GIVING RISE TO PAIN SIMULATING ANGINA PECTORIS*

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THE OCCURRENCE of gallstone disease with cardiac syndromes is now so well recognized that it would seem that further evidence on this relationship is hardly necessary. However, the frequency with which surgeons still see patients who have been classified as having serious cardiac disease, and who are simultaneously suffering from gallstone disease, but are denied surgical relief for the latter for fear of cardiac death, prompts us to make this report.

In 1909, Robert Babcock,¹ of Chicago, called attention to the frequent association of gallstone disease with heart disease. It is interesting to quote from his classic paper: "There is, however, another point of interest in this matter of the symptomatology of gallbladder disease, namely, the occurrence of disorders in the action of the heart, from arrhythmia and precordial oppression, without dyspnea, to demonstrable dilatation and incompetence, dating usually from some attack of biliary colic or acute cholecystitis, and thenceforth maintained by recurrences of the acute disturbance." He then concludes, after reporting 13 patients with this syndrome: "Experience has convinced me that the opening and draining of the gallbladder are attended with less danger when properly performed, even though myocardial incompetence be present, than is the doctrine of noninterference. Did time permit, cases could be cited which prove the peril to the patient from acute cholecystitis and fatal dilatation of the heart in cases with a history and symptoms of chronic cholecystitis, not to mention that from hepatic colic."

In 1935, Fitz-Hugh and Wolferth² pointed out that a "patient with gallstone disease may present such a convincing array of cardiac symptoms that the internist may wrongly condemn the sufferer to a 'life sentence' of cardiac servitude. In addition to this problem of mimicry . . . there is a growing conviction among internists and surgeons alike that chronic disease of the gallbladder may either initiate or aggravate actual heart disease—especially so-called coronary heart disease."

Fitz-Hugh and Wolferth found that in numerous instances flat or inverted T-waves in the electrocardiogram prior to operation became erect and normal subsequent to adequate biliary tract surgery. They concluded that "in the present stage of our knowledge it would be idle to speculate as to the nature of myocardial disturbances responsible for the remarkable electrocardiographic

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changes observed. It seems clear from the evidence, however, that not only may gallbladder disease injure the myocardium but that the process, at least to a certain extent, is reversible."

We have observed patients who have been decompensated for months and who had chronic auricular fibrillation restored to compensation and a regular cardiac rhythm with no change in the medical program following the simple removal of gallstones by cholecystostomy.

CASE REPORTS

Case 1.—Hosp. No. 19622: P. R., white, female, age 64, was admitted to the Hospital of the University of Pennsylvania, August 6, 1930, with a history of heart trouble over a period of eight years. She was short of breath, suffered from recurrent palpitation and right upper quadrant pain. For seven months she had been confined to bed. At varying periods she had had attacks of severe pain in the right upper abdomen associated with extreme nausea. She had taken digitalis for a number of years. She was markedly dyspneic and cyanotic. Examination of the heart showed this to be totally irregular. The heart was enlarged. The lungs were filled with moist râles at both bases. W. B. C. 9,200. There was ankle edema. There could be no doubt but that she had cardiac decompensation. Whether the right upper quadrant pain was due to gallstone colic or to distention of the liver was not immediately clear. A roentgenogram of the abdomen disclosed a large gallstone.

She was operated on August 9, 1930, three days after admission. The gallbladder was drained and the stone removed. On September 5, 1930, she was discharged from the hospital in good condition, and with complete cardiac compensation.

This patient was extremely ill on admission to the hospital. Two of my colleagues, one a surgeon and one a cardiologist, considered her too sick for operation when first seen. Three days later, with her general state unchanged, she was operated upon. The operation did not upset her; in fact, she began to improve markedly immediately thereafter.

When seen three months later she was free of dyspnea and cyanosis. Cardiac rhythm was normal and she was attending to certain of her household duties.

We have seen patients with long-standing serious cardiac disease made hopeless invalids by the aggravation of their cardiac symptoms and the additional symptoms imposed by a gallstone-bearing gallbladder or the presence of stones in the common duct.

Case 2.—Hosp. No. 42806: F. B., white, female, age 53, was admitted to the Hospital of the University of Pennsylvania, August 30, 1939. She was told that she had a "leaky heart" after peritonitis at age 25. She claimed that she had no very distressing symptoms until one and a half years ago when she had an attack of palpitation associated with weakness which lasted several hours. At the same time she began to have attacks of "indigestion" associated with abdominal cramps and diarrhea, and pain in the upper abdomen radiating around to the right side of the back. Some of the attacks had been severe enough to require morphine, although minor attacks occurred every few days. Each of these attacks was followed by increased palpitation and weakness. There was no doubt in her mind that these symptoms were augmented, if they were not initiated, by the attacks of abdominal pain. Her condition became such

that her physician placed her on a program of restricted activity. She had never been decompensated.

She was found to have an old "rheumatic" mitral valve disease (stenosis and insufficiency) with some myocardial degeneration; extrasystolic arrhythmia, with episodes of auricular fibrillation. In addition, she was found to have gallstones.

A cholecystectomy was performed September 6, 1939. Following cholecystectomy she had three attacks of paroxysmal auricular fibrillation, after which these disappeared.

She still has her heart disease but 15 months after operation she remains greatly improved, is able to resume many of her previous activities, and is not fibrillating. Although she still tires easily the attacks of "palpitation" occur only at rare intervals.

There have been indications in some of these patients that the symptoms of existing coronary disease can be made worse by superimposed gallstone disease and what is more surprising is that gallstone disease may, at times, initiate a train of events with symptoms which in many particulars resemble true angina pectoris. We have seen a number of the patients who for variable periods of time have been treated as cases of true angina pectoris by men considered competent in the field of cardiology and who, following the removal of a gallstone-bearing gallbladder or stones from the common duct, or both, have had complete freedom from their supposed anginal attacks.

Recently, Layne and Bergh³ reported that sudden distention of the common duct in man caused reflex spasm at the lower end of the common bile duct, which they designated as spasm of the sphincter of Oddi. They found that the spasm thus produced resisted levels of pressure within the common duct as high as 400 to 600 Mm. of water, and in some instances persisted for as long as four minutes.

The apparatus used in these experiments consisted of a large glass flask, or reservoir, of about 75 cc. capacity, connected by rubber tubing to the T-tube in the common duct of the patient. A glass Murphy drip bulb is used to demonstrate the flow of fluid within the system. The pressure developed within the common bile duct is registered by a glass manometer.

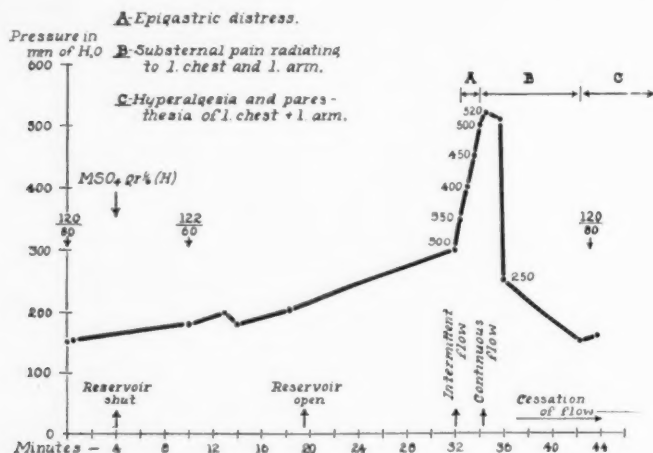
We wish to report the records of two patients in whom gallstone disease was associated with the symptoms of angina pectoris.

Case 3.—Hosp. No. 43748: S. L., white, female, age 48, was admitted to the Hospital of the University of Pennsylvania for the second time, February 23, 1940, with a history of attacks of severe precordial pain, occurring mainly at night but occasionally after meals, and accompanied by palpitation and dyspnea. The precordial pain radiated through to the back and down the ulnar aspect of the left arm to the finger tips. Following these attacks the patient noticed residual soreness of the precordium and paresthesias of the left forearm and fingers of the left hand. The pain was sometimes relieved by large doses of nitroglycerin.

The attacks began about five years previously, six months after a cholecystectomy performed elsewhere. There was no history of jaundice, acholic stools, nausea or vomiting. Until the last attack of pain a few days before entering this hospital, she had had no attacks of abdominal pain, all previous pain having been precordial in location. In spite of all previous therapeutic efforts, the attacks of pain had become more severe and more frequent. A diagnosis of angina pectoris had been made in another institution,

and a left stellate ganglionectomy had been performed. No relief was afforded by this procedure; in fact, the patient became much worse. Frequent attacks of pain were now brought on by the mildest exertion, even by eating. Many of the attacks came on at night while the patient was sleeping. She had lost 44 pounds in weight and had become practically bed-fast.

In December, 1939, she was first admitted to the Hospital of the University of Pennsylvania. At this time ballistocardiographic studies were made by Dr. Isaac Starr, which showed an abnormally low cardiac output, thought to be indicative of myocardial damage. Alcohol injection of the second, third, fourth and fifth thoracic sympathetic ganglia on the left side was done at this time. The patient was discharged and re-admitted February 23, 1940. During the interim she had become steadily worse. A few days before readmission she had experienced her first attack of definite abdominal



GRAPH 1.

pain. This pain had been located high in the epigastrium and right upper quadrant. However, at this admission, it was thought that her electrocardiogram for the first time showed evidences of coronary artery disease and localized myocardial damage.

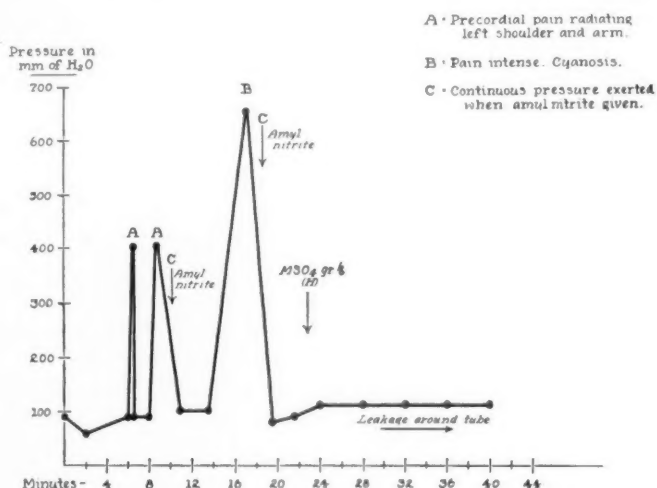
In view of the lack of results from previous therapy, and because of definite suggestion of a biliary tract origin for the patient's complaints, a celiotomy for exploration of the common bile duct was performed, March 22, 1940. A thick, kinked common duct was found, plastered with adhesions, and containing some "sand" but no stones. The duct was freed of adhesions, thoroughly irrigated and a T-tube left in place. Shortly after operation the patient declared that she was free of her former attacks of pain. She found that she could eat liberally without fear of discomfort. She was soon out of bed, and for the first time in five years, was able to walk about freely without recurrence of pain. Ballistocardiograms made at this time showed a normal cardiac output.

On the eighth postoperative day studies of common duct resistance were made (Graph 1). At the first severe distention of the common duct the patient complained bitterly of precordial pain, radiating down the ulnar aspect of the left arm, entirely similar to her previous attacks. She was very upset and had to be reassured that these pains were entirely a product of the procedures at hand, and not a recurrence of her old trouble. Distention of the common duct was repeated twice more on the same day, with exactly similar results. For several hours after the termination of these

BILE DUCT REFLEXES AND ANGINAL PAIN

studies, the patient complained of residual soreness in the precordium and of numbness and paresthesias of the left arm and hand. Four days later the experiments were repeated with similar results. At this time continuous electrocardiographic and ballistocardiographic tracings were made by Doctor Starr. Distention of the common duct was performed three times, and in each instance an anginoid attack was precipitated whenever the common duct pressure was raised to levels of 450 and 500 Mm. of water. The severe precordial pain subsided promptly upon release of the high ductal pressure, leaving residual precordial soreness, and paresthesias of the left arm and fingers of the left hand. The electrocardiographic and ballistocardiographic tracings showed nothing significant except for a slightly diminished cardiac output during the periods of severe distention.

The patient was shortly afterward discharged, symptom-free, and has remained so to date, despite removal of the T-tube from the common duct.



GRAPH 2.

Another patient in this series also gave a history of precordial anginoid pains suggesting coronary artery disease, prior to operation.

Case 4.—Hosp. No. 10770: K. T., white, female, age 45, was admitted to the Hospital of the University of Pennsylvania for the third time, December 9, 1940. She had previously had an appendicectomy and a hemorrhoidectomy, with uneventful recoveries. Her blood pressure readings had never exceeded normal figures. Since 1933, seven years before admission, she had experienced recurrent attacks of pain in the left side of the chest under the left breast with radiation to the left shoulder, produced by physical exertion or mental strain. She also had shortness of breath on exertion and swelling of the ankles. The attacks of this pain soon recurred so frequently that she could not perform her household duties and she became a semi-invalid. She was seen in the Robinette Foundation and a diagnosis of angina pectoris was made, on the basis of arteriosclerotic heart disease. In September, 1940, she first experienced an attack of intense pain in the right upper abdominal quadrant. The attack was accompanied by nausea and slight jaundice. Subsequently, she was studied in the gastro-intestinal department and a diagnosis of cholelithiasis was made. She had several more similar episodes of abdominal pain.

On December 13, 1940, cholecystectomy and choledochostomy were performed. Gallstones were found in the gallbladder, but exploration of the common duct revealed none. Following operation the patient was able to sleep on her left side for the first time in several years. She had no further attacks of pain, and when ambulatory was entirely comfortable and experienced absolutely no pain.

A pressure study of the common duct, similar to the one described above, was carried out on this patient (Graph 2). When the pressure was raised to a level of 400 Mm. of water pressure the preoperative anginal type of pain occurred. The pain ceased immediately upon reduction of the pressure. When the pressure was maintained at a high level, it was reduced gradually upon administration of amyl nitrite. It is interesting to note that the original anginal attacks were partially relieved by this drug. The ballistocardiographic tracing showed no abnormality before operation, after operation or simultaneously with the rise in pressure. Negative results were obtained with the electrocardiograph.

A cholangiogram was made through the T-tube and the films showed a narrowing of the lower end of the common duct. It is quite possible that an associated pancreatitis caused the slight jaundice. Four weeks after discharge the patient returned for another cholangiogram, and the duct was found to have become slightly larger. Follow-up examination, nine months later, revealed that this patient was completely relieved of all pain.

Bellet and Meade,⁴ in our laboratory, have attempted to produce significant changes in the electrocardiogram of the dog by distention of the gallbladder or common duct. They obtained no major changes in the electrocardiogram unless prior to distention of the biliary tract some minor abnormality had been produced in the coronary blood flow. When even a small coronary vessel had previously been ligated, abnormalities in rhythm and conduction were obtained.

The subject of viscerocardiac reflexes has been well summed up from the physiologic aspect by Scott and Ivy.⁵ They conclude that: (1) Changes in cardiac rate, rhythm, and output can be caused by distention of the common bile duct in dogs; (2) such changes are inconstant, variable, and unreliable; (3) success or failure in the production of such changes by common duct distention depends on the presence or absence of functional or organic cardiovascular abnormality at the time the distention is carried out.

Barker, Wilson and Coller,⁶ and others, have reported cases of abdominal disease simulating coronary disease. In three of their four cases, the electrocardiogram was normal. In the fourth, it showed definite evidence of coronary artery disease. All were cases of cholelithiasis and cholecystitis; and all were relieved of their symptoms by operation.

Recently Gilbert, and his associates,^{7, 8} have published important contributions in this field. They have shown that there is a decrease in coronary blood flow upon distention of the gallbladder, or distention or irritation of its ducts. Gilbert has called attention to the fact that both clinical and experimental evidence indicates that stimuli originating in the gallbladder may cause a decrease in the coronary blood flow which results in a disproportion between blood supply and blood needs similar to that which occurs when intrinsic anatomic changes are present in the vessel walls. In the one instance pain

is the result of spasm induced by extrinsic autonomic stimuli, in the other the disproportion becomes evident when additional demands are made upon the restricted supply of blood in the coronary vessels. The degree to which intrinsic and extrinsic factors are involved in bringing about a restriction in coronary blood flow without doubt varies greatly in different patients and accounts for the variability of the preoperative and postoperative symptoms. While the intrinsic factors may be irreversible, the extrinsic factors are reversible provided their cause can be eradicated.

Distention of the common bile duct in the presence of muscular irritability at the lower end of the duct will cause reflex spasm in this region and physiologic blockage of the duct. It is important to the investigator to realize that after the administration of morphine sulphate, gradual distention of the duct such as obtains during experimental determinations of sphincter resistance or perfusion pressure also causes reflex spasm nearly as marked as that produced by rapid distention under the same conditions. For this reason, values for perfusion pressure obtained after the administration of morphine sulphate necessarily have a wide range, from the levels of pressure at which definite flow is first noted, to the high levels of pressure needed completely to overcome the vicious cycle of reflex distention-spasm. After morphine sulphate, then, even small increments of common duct pressure will promptly produce reflex spasm, which in turn raises the perfusion pressure level necessary to overcome resistance to flow in the common duct. To overcome resistance at this new level, additional increments of pressure are necessary, but these, by their distending effects, produce still more spasm and increase the perfusion pressure value still more. Thus a staircase phenomenon of increasing perfusion pressure values is produced before peripheral ductal resistance is completely overcome at a very high level of pressure.

The observations of Best and Hicken,⁹ Doubilet and Colp,¹⁰ and McGowan, and his associates,¹¹ demonstrate that degrees of irritability in the duodenocholedochal region sufficient to cause biliary tract pain are often encountered in certain types of patients. Layne and Bergh have reported no cases in which this irritability was of sufficient magnitude that mere sudden distention of the common duct in these patients created severe reflex spasm, and a high degree of mechanical obstruction of the common duct. In the present studies, comparable degrees of spasm have been produced by sudden distention only after the administration of morphine sulphate.

SUMMARY

We believe, however, that these are the first reported patients in which anginal attacks have been consistently reproduced experimentally in man, by distention of the common duct.

It can now be safely assumed that gallstone disease or disease of the common duct may aggravate the symptoms of preexisting heart disease. Reflexes arising in the extrahepatic bile passages may at times bring about

a restriction in coronary blood flow which produces the symptoms of angina pectoris. When the extrinsic factors giving rise to these reflexes are removed, the anginal symptoms disappear. Similarly such reflexes may further decrease the coronary blood flow brought about by intrinsic changes in the coronary vessels. While adequate surgery does not completely relieve the patient of his cardiac symptoms, some measure of relief is nearly invariably obtained.

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- ¹¹ McGowan, J. M., Knepper, P. A., Walters, W., and Snell, A. M.: Surg., Gynec., and Obstet., **66**, 979, 1938.

DISCUSSION.—DR. CHARLES G. MIXTER (Boston, Mass.): Doctor Ravdin has brought clearly to our attention a problem that is always difficult—has the patient biliary tract disease, coronary disease, or has he both? Furthermore, he has emphasized the part that biliary tract disease may play in the aggravation of the concomitant heart disease. Finally, he has been able to reproduce in patients in whom the common duct pathology has been removed, the anginal symptoms by distention of the common duct.

Left-sided pain in biliary tract disease is usually explained by pancreatitis, or an extension of the pericholecystic disease to the left side. Rarely, pain may occur on the left side without extension of the inflammatory process. On embryologic grounds, the common duct must be assumed to have a bilateral innervation. This would explain the occurrence of left-sided pain.

Recently, Doctors Fine and Starr, of our clinic, have reported two cases of crossed pain in biliary tract disease. The first patient was a female, age 45, with an eight-year history of severe stabbing pain, starting in the epigastrium and radiating around the left costal margin and to the left scapula, occasionally to the left shoulder, arm and finger tips. The attacks were not related to food, exercise, or rest. A cholecystectomy had been performed six years previously. The gallbladder had contained stones. The common duct was normal to palpation and was not opened. Recurrence of attacks of pain in the chest led to a diagnosis of angina. There were no jaundice and no gastro-intestinal symptoms. The electrocardiogram and glucose tolerance curve were normal. Duodenal drainage yielded crystals. At operation a single pea-size stone was removed from the common duct. She has been symptom-free for two years.

Case 2 was a female, age 71. Her first attack occurred one week before entering the hospital, and she had had nightly seizures of girdle pain, of equal intensity, on both sides. The electrocardiogram showed a probable intraventricular block. The icteric index was 15. Cholecystogram showed cholelithiasis. At operation, a small gallbladder, containing stones, was excised, and stones were removed from the common duct. During convalescence clamping of the common duct drainage tube initiated pain. At other times she was symptom-free. A cholangiogram revealed a small residual stone. To establish a relationship between the common duct stone and the preoperative left-sided pain, saline solution was injected both slowly and rapidly, with a reproduction of the pain along the left costal margin and in the left scapula. There was no pain reference to the epigastrium or right side. It was

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felt this procedure forced the calculus into the duodenum, as a subsequent cholangiogram failed to show a stone. Removal of the tube was followed by rapid closure of the sinus, and there has been no recurrence of the attacks of pain.

There is a small, but distressing, group of cases in whom symptoms persist after cholecystectomy with or without a demonstrable lesion of the common or hepatic ducts. In these, severe attacks of pain persist without associated fever, jaundice or elevation of white blood cells. Dyskinesia of the biliary tract has been discussed in the literature for some years. Dilator drugs usually give transient relief and gradually, over a period of months, cessation of symptoms occurs. Occasionally, one sees a case characterized by more severe pain suggestive of definite biliary colic, in whom benzedrine or atropine give no relief, and in whom the symptoms persist.

An example of this type of case occurred in an intelligent woman of about 40. Following cholecystectomy for stones, colicky pain without jaundice recurred. A number of months later her common duct was explored but no pathology was demonstrated. Her convalescence was uneventful, except that every time the common duct tube was clamped an attack of colic was brought on. After prolonged drainage the common duct tube was removed, the sinus healed readily, but attacks persisted. Finally, a dorsal sympathectomy with resection of the great splanchnic nerve and removal of the lower three dorsal ganglia was undertaken by Doctor Smithwick. The patient has been free of symptoms for over two years. We have had two other similar cases in whom dorsal sympathectomy has afforded relief, but the time that has elapsed since operation has been too short to venture the assertion that they have been cured.

DR. GEORGE J. HEUER (New York): Doctor Ravdin's paper has brought up a great many interesting questions in this matter of association between gallstone disease and heart disease.

One of the interesting things that we found in a study of a fairly large series of cases of gallstone disease was that a rather high percentage of the patients with gallstone disease, who arrived at age 50 or over, had cardiorenal disease and hypertension. In comparing this group of cases with such information as we could get from life insurance statistics, it was evident that patients in our series who were over 50, and had gallstones, had in a much higher percentage of complications, if you want to call it that, such as heart disease and hypertension, than we could find occurring in the normal population of the country in the same age-group. I hope that Doctor Ravdin will indicate whether that has been his experience.

The question again arises as to whether gallstones in some way provoked these conditions in a higher percentage of cases or whether patients with these conditions were more prone to gallstones. This is very difficult to get at, of course, and I doubt whether one could arrive at a definite answer, but, certain it is, I think from our series of cases—and they number some 1,200—we have studied—that there is a higher incidence of these cardiorenal conditions with hypertension in the age-groups over 50, than occur in the population ordinarily.

DR. FRANK K. BOLAND (Atlanta, Ga.): We have had some reference this morning to historical medicine, and it is with the object of reminding you of another historical fact that I rise. This historical fact also illustrates to us the diagnostic clinical acumen of some of the forefathers in medicine, who worked without electrocardiograms and without roentgenograms.

You will recall that John Hunter died in a hospital committee meeting from an attack of angina. Hunter's physician was none other than Edward Jenner. Hunter was known to have these heart attacks, but Jenner insisted that he also had gallstones. The point I wish to give you is that the autopsy revealed that Jenner was right and that John Hunter had gallstones and also had coronary sclerosis.

DR. JOHN A. WOLFER (Chicago, Ill.): Along the line of Doctor Ravdin's presentation, I want to put two side-lights on record. One was in a woman of about 60 years of age, upon whom I had performed a radical mastectomy. A short time after the

operation she developed typical precordial pain, radiating down the left arm, associated with some dyspnea and slight cyanosis. The electrocardiogram was typical of coronary disease, and as the symptoms progressed, further study revealed that she had a small diaphragmatic hernia, and when the diaphragmatic hernia was filled with food she had the typical electrocardiographic findings of coronary disease, and when the gastric pouch was empty her electrocardiogram was perfectly normal.

The other is a reversal of the syndrome exemplified by this case. A man from South Carolina was diagnosed as having a fulminating acute cholecystitis, with fever of 102° F. and leukocytosis of 22,000. He was seen by a surgeon in that community, who refused to operate upon him because of the severity of the symptoms. He recovered, went to Florida, and I saw him the next spring.

His history was perfectly typical of chronic cholecystitis, having right upper abdominal pain, distress after eating, and nothing which would suggest cardiac disease. A study of the gallbladder revealed it functioned normally. Further study revealed nothing organic in his gastro-intestinal tract. The next morning he was found dead in bed. At autopsy, there was found an enormous scar in the heart, which I can only describe to you as looking like the bottom of a white china saucer. Almost the entire myocardium had been replaced by a scar tissue. Yet the man gave a typical gallbladder story, so much so that Doctor Case, when he examined his gallbladder, he made a little note after his interpretation saying: "I hope that my negative cholecystographies will not deter Doctor Wolfer from taking this man's gallbladder out." Yet, he had no gallbladder disease, and his history would indicate he did have the effort syndrome. In other words, he became distressed when walking and developed indigestion and pain with walking. But beyond that there was nothing.

By the way, the electrocardiogram was reported: "Nothing significant found."

DR. HARRY B. ZIMMERMANN (St. Paul, Minn.): We have sufficient diagnostic machinery for limited diagnosis of gallbladder disease, but quite often the question comes up as to whether one wants to use surgical therapeutics in the presence of cardiac disease. I am fairly convinced that there is something to the modern idea that atheromatous disease has a great deal to do with metabolic reverses. Quite often disease of the extrahepatic biliary tract, besides gallbladder, can aggravate such disturbances in the metabolism, and I would not hesitate in persons with fairly definite atheromatous disease and cardiac disease to use surgical therapeutics.

DR. I. S. RAVDIN (closing): I think the observations that Doctor Mixer and Doctor Smithwick have made in the patients with dyskinesia are very important observations, because everyone interested in the surgery of the extrahepatic biliary passages must have seen a group of patients who continued to have colic, even though there remain no stones in the common duct.

I am sure that Doctor Heuer's observations are correct ones. There is a higher incidence of cardiac disease in patients with biliary tract disease, patients with stones, and a greater incidence of hypertension in the patients past 40 years of age—I believe Doctor Heuer said 50—than there is in the population at large.

Doctor Wolfer's observation merely accentuates the fact that we must be exceedingly careful in attempting to arrive at an accurate diagnosis. We have, however, seen two additional patients whom, had we followed our inclination, we might not have operated upon, and the patients would certainly have died; two patients with acute obstruction of the common duct who immediately went into shock, so that it was impossible to record either their systolic and diastolic blood pressure. They were operated upon under continuous spinal anesthesia at a time when blood pressure could not be recorded. Immediately after drainage of the common duct the blood pressure returned so that it could be recorded.

This merely goes to show that both of these individuals were diagnosed, initially, as having enormous cardiac infarctions. Both of these individuals showed evidence of preexisting cardiac infarction. Both of them survived operation well, and have done well since operation. It merely further emphasizes the fact that one can, by having reflexes which arise in the extrahepatic biliary passages, so accentuate intrinsic existing disease of the coronary vessels as to set up a train of events which produces nearly complete

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cardiac incompetency and which can be relieved providing the mechanism which initiates these reflexes is relieved.

I am perfectly sure that many of these individuals that are not now being operated upon should be, and our experience has shown that the risk of operating upon these individuals, properly prepared before operation and properly taken care of during operation, is not great. At the present time everyone is being operated upon with continuous spinal anesthesia, which I believe, in this group of patients, provides the greatest safeguard.



WAR SURGERY

The outstanding feature of the surgery of the present war, as compared with that of the last, was the almost complete disappearance of the ward dressing trolley and the war gas apparatus. The appalling pain caused by the daily, or twice daily, dressings had gone, and in its place was the modern technic of excision and fixation. Fixation was practically always by plaster of Paris, although in the wounds of the thigh in fat women complete fixation by this means was an extreme difficulty. An addition to the technic was the use of sulfanilamide by packs or in powdered form, or by insufflation on the surface of the wound; although the use of sulfanilamide had helped to prevent sepsis in some cases which had not come for operation for four to eight hours after the infliction of the wound, nothing could replace the perfect excision of the wound, which was the essential point in the treatment. Nothing was so criminal as to suggest that the excision could be done badly so long as sulfanilamide was used. The main problems met with now were shock, for which fortunately the treatment was almost standardized; the prevention of sepsis, which depended largely on the excision of infected and dead tissues and the wide opening-up of tissues which had become infected; and fractures of the pelvis, which had occurred more frequently than normal owing to the falling in of bombed houses. In many of these cases of fractured pelvis there was a rupture of the urethra, and it would be well if agreement could be reached on the ideal treatment of this complication.

—T. P. McMurray at a meeting of the Liverpool Medical Institution as reported in the British Medical Journal.

THE SURGERY OF CARCINOMA OF THE PANCREAS AND AMPULLARY REGION*

REPORT OF SIX ADDITIONAL CASES

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THE SURGICAL TREATMENT OF CANCER of the pancreas and ampullary region has received recently increased attention. The successful removal of large portions of the pancreas, together with the ducts,^{5, 9} has been reported by various authors. This experience has modified some of the established concepts of the physiology of the pancreas, and particularly concepts regarding the indispensability of the external secretions of this organ.

The successful removal of cancers in this hitherto inaccessible region has encouraged internists to review again the early signs and symptoms of this disease,¹ in the hope of finding more patients with the disease still in an operable stage. Since no one individual has acquired a large experience in the management of these patients and since the surgical technic is still in the developmental stage, the authors wish to present six additional cases for discussion.

CASE REPORTS

Case 1.—*History No. 7023: W. P., male, age 48. Admitted June 18, 1932. Six months—attacks of subscapular pain; five months—glycosuria; three months—abdominal pain on reclining, relieved by standing; two months—constipation, anorexia, weakness, weight loss. Small left abdominal tumor. Diagnostic exploration, cancer, body of pancreas. Splenectomy and subtotal resection of pancreas. Recovery. Died five months postoperative.*

Chief Complaint.—(1) Pain in the back and stomach. (2) Weakness.

Present Illness.—Onset January, 1932, with dull, nonradiating, left subscapular pain in attacks lasting one to two days, increasing in frequency to admission. In March, 1932, he experienced a sensation of heaviness in the upper abdomen, described as "feeling as though the stomach were all cramped-up." This pain was relieved by standing up, leaning forward or flexing the thighs on the abdomen. This sensation, which he felt during the whole day, had recently been waking him from sleep at night. There had been increasing constipation and weakness with a weight loss of 15 pounds in two months. In February, 1932, during an insurance examination, a small amount of sugar was found in the urine and this had been verified on subsequent tests.

Past History was negative except for bleeding hemorrhoids.

Physical Examination.—Showed a well-developed but emaciated man, with pale and sallow complexion. "He had the general appearance of a person suffering from malignancy." General oral sepsis and carious teeth. Abdomen showed slight tenderness in the epigastrium and just to the left of the midline was an indefinite small palpable tumor mass. Remainder of examination was irrelevant.

* Read before the American Surgical Association, Cleveland, Ohio, April 6-8, 1942.

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Laboratory Data.—Fasting blood sugar: On admission—79 mg.; two hours after ingestion of 50 Gm. of glucose—128 mg. Repeat fasting—130 mg. Urine: Normal, no sugar. Blood: R.B.C. 3.5 Hemoglobin 95 per cent. W.B.C. normal. Repeated stool examinations showed presence of bile and no blood or other abnormalities. Gastric analysis: Fasting—HCl. 1 cc.; after histamine—HCl. 10 cc. Roentgenograms of the gastrointestinal tract and lumbodorsal spine negative.

Operation.—S.C.H.: July 6, 1932.

Preoperative Diagnosis.—Retroperitoneal tumor.

Postoperative Diagnosis.—Carcinoma of the body of the pancreas.

Procedure.—Splenectomy and subtotal excision of the pancreas.

A left upper rectus incision was made. On exploring, it was found that a dense mass, measuring 4-5 cm. in diameter, lay directly over the aorta in the midline at the level of the pancreas. By dividing the gastrocolic omentum so as to give exposure to the pancreatic region, it was found that this mass lay in the body of the pancreas, and that excision of it meant an excision of the pancreas. An attempt was made to work around the mass from above and below, but it was found quite impossible to establish the exact line of cleavage. Consequently, the spleen was freed from the parietal peritoneum inward toward the midline, the tail of the pancreas elevated and then dissection proceeded with, posteriorly, until the pancreas was freed up as far as the underlying superior mesenteric artery. Dissection was then started at the head of the pancreas and it was found possible to get between the tumor mass and its attachment to the duodenum. The pancreas was divided between crushing clamps, leaving a ribbon of pancreas 1 cm. wide on the duodenum. The dissection then proceeded to the left and the splenic vein was identified as it entered the portal vein and largely surrounded by tumor tissue. The portal vein was isolated from the tumor mass and a clamp placed across the splenic vein at its junction with the portal vein and divided. Dissection was then carried medialwards, the mass dissected off the hepatic artery and the superior mesenteric artery, the splenic artery then being ligated and divided and the mass removed. The large intestine covered the raw area. The wound was closed without drainage.

Postoperative Course.—The patient had a rather stormy course for the first 12 hours postoperatively, but thereafter made a rapid and steady gain. Repeated urinalyses before and after operation, including routine diabetic fractional specimens four times daily, revealed only a very infrequent small trace of sugar. Repeated stool examinations postoperatively revealed no evidence of failure to digest fats. The patient was discharged from the hospital 17 days postoperative, with instructions to follow a diet of 70 Gm. protein, 100 Gm. fat and 200 Gm. carbohydrate. He tested his own urine. Follow-up on this diet revealed that he gained weight, had an excellent appetite and no difficulties with digestion or sugar in the urine. He died five months postoperative, probably of metastases, although no postmortem examination was obtained.

Pathology Note.—The pancreatic tissue was exceedingly firm and on section its normal architecture was entirely lacking, being replaced by coarsely granular, yellow-gray tissue. There were no areas of hemorrhage or calcification. There was one large lymph node found to contain tumor tissue. Microscopic examination confirmed the gross impression of an extensive destruction and fibrosis of pancreatic tissue. Even large blood vessels were occluded by fibrosis. The tumor was an adenocarcinoma invading lymph nodes and along nerve sheaths. There were numerous mitotic figures and a tendency to acinar formation.

Comment: This patient was the first of our series, and while a tentative diagnosis of carcinoma of the pancreas was made, it was by no means certain. He had a six-months history of pain, now recognized as characteristic of carcinoma of the pancreas; namely, pain worse on reclining and relieved by leaning forward or relaxing the abdomen. In spite of removal of all but a small fraction of the pancreas he showed no sugar and gained weight on a

mild limitation of diet. There were no evident disturbances of fat metabolism. He had lymphatic metastases at operation, and while the cause of death is unknown, it was likely due to extension of the tumor. An earlier diagnosis or exploration might have yielded a successful result.

Case 2.—History No. A94807: L. P., male, age 60. Admitted July 17, 1939. Two months—itching, jaundice, weight loss 26 pounds. Transduodenal resection cancer of ampulla, with reimplantation of common and pancreatic ducts. No evidence of recurrence two years eight months. Living and well.

Chief Complaint.—Itching.

Present Illness.—Began a little more than two months before admission with itching, shortly followed by jaundice, clay-colored stools and dark urine. Although his appetite and digestion were said to have remained excellent, he had lost 26 pounds weight. He had no pain.

Physical Examination.—Positive findings were a deeply jaundiced skin, with many small red annular lesions; eyes sunken, sclerae icteric, retinal arteriosclerosis; mouth septic with advanced caries; abdomen slightly distended and tympanitic; slight tenderness in right upper quadrant, where a smooth, firm liver edge was felt 2 cm. below costal margin. The spleen could be felt on deep inspiration. He also had bilateral inguinal herniae, and a diffusely enlarged prostate.

Laboratory Data.—Urine: Normal except for bile 4+. Blood: Normal. Icteric index: 60 units. Liver function (bromsulfalein): five minutes—85 per cent dye retention, 30 minutes—45 per cent dye retention. Stools: Normal except for absence of bile. Roentgenologic gastro-intestinal series and intravenous cholecystogram negative. *Impression.*—Carcinoma of head of pancreas or ampulla.

Operation.—A.W.O.: August 2, 1939. Transduodenal Excision of Carcinoma of Ampulla of Vater. The liver was found to be enlarged; the surface was rough and granular in appearance with some cirrhosis. The gallbladder was markedly dilated and the common duct 2.5 cm. in diameter. Palpation revealed no evidence of stone. The only abnormal finding, and that indefinite, was a small soft mass in the region of the ampulla. The second portion of the duodenum was mobilized and a longitudinal incision made in it opposite the ampulla. A flat, cauliflower growth was found arising from the ampulla. It was 1 cm. in thickness and 3 cm. in width, with a papillary structure. A portion of this was excised for biopsy which was reported benign. A probe could be readily passed into the pancreatic duct but the common duct was completely obstructed. The tumor was resected by a circular incision 3 cm. in diameter, the base of the tumor being 1 cm. in diameter. The incision was carried through all layers of the duodenum and thence across the ducts at a depth of 2 cm. As the common duct was cut there was a free flow of bile. The cut ends of the common and pancreatic ducts were then mobilized and sutured together with fine interrupted silk. The edges of the duodenal mucosa were then sutured to the common and pancreatic ducts, forming a slight pit. It was necessary to do some slight mobilization of the duodenal mucosa in order to accomplish this. The opening in the duodenum was then closed in the usual manner. No drains were used.

Postoperative Course.—This was smooth and he made an uneventful convalescence. A postoperative check-up film was taken showing the defect in the duodenum. Repeated roentgenograms since have shown no evidence of recurrence, and the patient continues in good health with no complaints.

Pathology Note.—The biopsy had been taken from the surface of the cauliflower tumor. The pedicle was firm and extended into the common duct, completely occluding it and invading the wall of the pancreatic duct. Microscopic examination revealed the base of the tumor to be adenocarcinoma, Grade II, apparently arising in the base of a papilloma. There appeared to be an adequate margin excised.

Comment.—This patient had a papillary cauliflower tumor apparently arising within the common duct, since this was completely occluded. The pancreatic duct was involved but still patent. The soft, flattened, sessile character of this tumor permitted it to blend with the duodenal wall in such a manner that it was not visualized roentgenographically. While the tumor was completely removed, as shown by histologic examination, and there has been no evidence of recurrence in two years and eight months, nevertheless, the question may be raised as to whether this type of local excision was adequate treatment of this condition. This was the only patient in this series with the classical syndrome of painless jaundice.

Case 3.—*History No. B6323: J. B., male, age 70. Admitted May 16, 1941. One year—anorexia, nausea, vomiting and weight loss. Three weeks—pain and jaundice; hepatomegaly, epigastric mass; roentgenographic deformity of duodenum; two-stage operation: Cholecystojejunostomy entero-enterostomy, resection of duodenum and head of pancreas, gastrojejunostomy. Recovery. Sudden death three months postoperative.*

Chief Complaint.—Abdominal pain and nausea.

Present Illness.—He first came to the Medical Clinic in July, 1940, at which time he was examined to determine the cause of his complaint of anorexia, nausea, vomiting and weight loss of 20 pounds. Impression was that of generalized arteriosclerosis and hypertension, aneurysm of abdominal aorta, and probable duodenal ulcer. Laboratory data was essentially negative, including gastric analysis. At that time he had a question of clay-colored stools for a short period. Roentgenologic examination was advised but the patient did not return until ten months later, May 16, 1941. During this interval he continued at his work but suffered off and on with dull intermittent abdominal pain.

Three weeks before admission he noticed jaundice for the first time, which became progressively more intense, followed by itching. At the same time the dull intermittent epigastric pain became more severe. The abdominal throbbing which had been present since July, 1940, remained the same. He became constipated and his stools were white, although his diet had been restricted to skimmed milk, eggs and fat-free foods. With the onset of the present illness he developed shortness of breath and dyspnea. He had lost 15 pounds in the past month.

Physical Examination.—Showed a chronically ill, emaciated, jaundiced elderly man. Positive findings were oral sepsis and carious teeth; a slightly distended abdomen with audible and visible peristalsis; dilated epigastric veins; liver extended to anterior superior iliac spine and was nontender, with a sharp, firm, irregular edge. In the mid-epigastrium there was a hard mass adjacent to the aorta. There was pitting edema of the feet with generalized arteriosclerosis.

Laboratory Data.—Blood: R.B.C. 3.06; W.B.C. and smear normal. Blood sugar (fasting): 83 mg. per cent. N.P.N.: 33 mg. per cent. Icteric index: 100 units. Van den Bergh: Direct reaction, 20 seconds; indirect reaction, 2.7 mg./100 cc. Prothrombin time normal. Serum proteins: 5.63 mg. per cent; serum albumin: 3.03 mg. per cent; serum globulin: 2.60 mg. per cent. Stools: Clay-colored, bile and blood negative. Blood studies (fats): Serum titrated fatty acids: 10.0; serum lipoid phosphorus: 8.0 mg. per cent; serum total cholesterol: 159 mg. per cent; serum unesterized cholesterol: 53 mg. per cent. Liver function (bromsulfalein): 20 minutes—50 per cent dye retention. Gastric analysis: Free HCl—33 units; after histamine, free HCl—74 units.

Roentgenologic Examination.—(1) Narrowed and deformed distal first and proximal second duodenum (probably primary carcinoma of biliary tract, with secondary involvement of duodenum); (2) diverticulosis of colon; and (3) atypical small intestinal pattern (deficiency state).

Operation.—A.W.O.: May 27, 1941: Cholecystojejunostomy, Entero-enterostomy. An

upper right rectus incision was made. The liver extended to the crest of the ilium and was a deep purplish color mottled with yellow, with a coarse granular surface. The gallbladder and common duct were markedly distended. A movable tumor was found in the head of the pancreas about the size of a tennis ball. There was no evidence of metastasis. The jejunum was divided about three feet below the ligament of Treitz and an end-to-side anastomosis was performed, leaving a proximal blind end about 18 inches in length which was anastomosed to the fundus of the gallbladder. The wound was closed without drainage.

The patient made an uneventful recovery, and in four days the icteric index had dropped to 15, and bile was present in the stools. The patient's appetite improved, he put on weight, was ambulatory, and his deficient state seemed reasonably well corrected. Bromsulphalein liver function test showed 4 per cent dye retention in 30 minutes.

Second Operation.—A.W.O.: July 16, 1941: Resection of Duodenum, Head and Part of Body of Pancreas, with Posterior Gastrojejunostomy. An upper right rectus paramedian incision was made. The adhesions from the previous operation were readily divided and the duodenum was exposed. The tumor was found to be about one-half the size it had been on the previous operation and it was more freely movable. The lateral border of the duodenum was readily mobilized and turned up off the vena cava, exposing the under surface of the pancreas. The inferior portion of the duodenum was readily dissected free, passing underneath the colic vessels in the mesentery and entering the free peritoneal cavity at the ligament of Treitz. No bleeding was encountered during this part of the procedure. The right gastric and gastroduodenal arteries were ligated and the pylorus was mobilized, clamped and divided. The jejunum was picked up at the ligament of Treitz. The anastomosis to the gallbladder had been far enough down the bowel so that there was ample jejunum. A posterior gastrojejunostomy was performed in the usual manner. The common duct was then isolated, divided and triply ligated with silk. The ligatures were spaced 0.5 cm. apart, the proximal being not too tight and the distal transfixed. The dissection was then carried along the portal vein from below upward, ligating the small tributaries as well as the inferior pancreatic duodenal artery. The dissection was carried through the pancreas on the left of the portal vein. The pancreatic duct was separately ligated. The pancreas was very fibrosed and indurated. Two mattress silk sutures were placed in the cut end of the pancreas. The duodenum was clamped in its third portion, divided and inverted with a Parker-Kerr stitch, reinforced with interrupted silk sutures. A Penrose sheath-drain was placed to the cut end of the pancreas. It was an easy operation; the patient stood the procedure well, and left the table in good condition.

Postoperative Course.—The convalescence was uneventful until the seventh postoperative day, when what appeared to be a clean wound broke down. There was marked tryptic activity of the secretion and superficial suction was used. Four days later bile suddenly began to drain and continued for two weeks. Suction was maintained, the wound slowly healed and the patient was discharged on the fortieth postoperative day. He had a fair appetite and slowly gained weight on a low fat diet. He had no diarrhea or glycosuria but occasionally complained of transient, vague lower abdominal pains. He appeared to be doing well when he suddenly died, three months after operation. No postmortem examination was obtained.

Pathology Note.—The tumor in the head of the pancreas was 2×3 cm. in diameter and occluded both the pancreatic and common ducts. In and around the main tumor were numerous small cysts filled with clear yellow gelatinous material. The duodenal mucosa was not involved. Microscopically, the tumor was made up of cells varying in size and shape invading the stroma of the gland. Many of the cells were secreting mucus and some of the acini formed by the invading cells were filled with mucus. Some of the tumor cells were found invading the parenchyma of the regional lymph nodes by direct extension and by metastasis. *Pathologic Diagnosis.*—Mucus secreting adenocarcinoma of the head of the pancreas, with metastases to local lymph nodes.

CARCINOMA OF PANCREAS

Comment.—This patient had symptoms severe enough to bring him to the clinic one year before admission. Roentgenologic examination was advised but he did not return. Since there was a marked deformity of the duodenum on admission it is likely that a diagnosis could have been made earlier. He had severe liver damage, with a high icteric index and low protein previous to the first stage. His general condition was markedly better when the second stage was performed. The drain left in at the second operation undoubtedly contributed to the wound disruption, since there was active tryptic secretion in the wound. There was bile drainage and clay-colored stools for two weeks, indicating that the common duct may also have been digested in spite of a double ligation and transfixion with silk. Postoperatively, he had no glycosuria or diarrhea and was gaining weight. Cause of sudden death unknown. He had severe arteriosclerosis and mild decompensation. Lymphatic metastases were also found in the specimen.

Case 4.—*History No. B4275: H. M., male, age 44. Admitted June 10, 1941. Three months—gaseous indigestion and constipation. Five weeks—dull epigastric pain and fullness. Ten days—lumbar pain. Two days—jaundice, ten pounds' weight loss. Two-stage operation. Cholecystojejunostomy, entero-enterostomy; resection duodenum and pancreas, gastrojejunostomy. Recovery. Living and well nine months.*

Chief Complaint.—Jaundice.

Present Illness.—Thirteen weeks before admission he developed an upper respiratory infection accompanied by constipation. This was followed by a gradually increasing sensation of epigastric fullness, indigestion and belching, relieved by bisodol. All of these symptoms increased and were worse two hours after eating. Five weeks before admission he consulted his physician who made a tentative diagnosis of peptic ulcer and gave him a diet. His symptoms increased in severity, and ten days before admission he developed pain in the lumbar region at the same time as the epigastric fullness. Two days before entry he noted jaundice and clay-colored stools. During the past three weeks he had noticed increasing fatigue and had lost ten pounds' weight. **Family History.**—Mother died of diabetes.

Physical Examination.—Showed a heavy, well-nourished individual, not appearing acutely or chronically ill. There was a slight icteric tint to the skin, and the liver edge was just palpable below the costal margin. Otherwise negative.

Laboratory Data.—Urine: Bile positive. Liver function (bromsulfalein): July 6, 1941—five minutes—45 per cent dye retention; 30 minutes—22 per cent dye retention. July 18, 1941—Blood fats: Serum titrated fatty acid: 19.5 mg. per cent per liter; serum lipid phosphorus: 11.1 mg. per cent; serum total cholesterol: 245.0 mg. per cent; serum unesterized cholesterol: 72.0 mg. per cent.

Roentgenologic Examination.—This showed cardiac enlargement; calcified pulmonary tuberculosis and hilar lymph nodes; old pleurisy, left base. Duodenal loop wide, as if there were a tumor in the head of the pancreas. The lesser border was more smoothly outlined than the greater border of the curve; there was a question also of duodenal ulcer.

Operation.—A.W.O.: June 23, 1941: Cholecystojejunostomy; Entero-enterostomy. A right upper rectus incision was made, and the gallbladder and common duct were found to be greatly dilated. There was a firm mass, 4 cm. in diameter, in the head of the pancreas in the region of the common duct medial to the second portion of the duodenum. The tumor was freely movable. There was some thickening in the pylorus suggesting an ulcer. The jejunum was divided and an end-to-side anastomosis was performed. The blind end was then anastomosed to the fundus of the gallbladder in the usual manner.

Postoperative Course was uneventful. His symptoms disappeared, his appetite improved, and the laboratory findings were all normal.

Second Operation.—A.W.O.: July 21, 1941: Resection of the Duodenum and Head of the Pancreas with Posterior Gastrojejunostomy. A right rectus incision, excising the old scar, was made. The tumor was found to be reduced to almost half the size found at the previous operation. The peritoneum was incised along the lateral border of the duodenum which was reflected medially with the head of the pancreas. Considerable bleeding was encountered in this usually avascular area. A very liberal collateral circulation seemed to have been developed. The right gastric and gastroduodenal arteries were then ligated and the pyloric region was mobilized, clamped and divided. The jejunum was then brought up through the transverse mesocolon and a posterior gastro-



FIG. 1.—Case 4: Air in the extrahepatic biliary passages.

jejunostomy was performed in the usual manner. The common duct was then divided and triply ligated with silk 0.5 cm. apart, the distal suture transfixing the duct. Inadvertently, the intravenous therapy had failed to function properly and the patient went into shock. Since the most difficult part of the operation remained it was necessary to cease operating until his circulatory collapse had been corrected. The last portion of the duodenum was found to be tied down by adhesions and there was difficulty in freeing up this portion. This was further complicated by the fact that the patient was very obese and the mesentery to the small bowel greatly thickened. In order to get well around the tumor it was necessary to leave a very short stump of the duodenum for inversion. In retrospect, this part of the operation would have been much easier if the division had been made in the jejunum below the ligament of Treitz rather than in the duodenum. The dissection was then carried along the portal vein, ligating its tributaries and the inferior pancreaticoduodenal vessels. The body of the pancreas was unusually hard. The pan-

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creatic duct, which was dilated and filled with secretion, was separately ligated. A partial V-excision transversely was used and the end of the pancreas closed with interrupted mattress sutures. The wound was closed in the usual manner with interrupted silk. A rubber sheath drain was placed to the cut surface of the pancreas.

Postoperative Course was complicated by a right lower and middle lobe atelectasis. However, following aspiration his vital signs were essentially normal on the second postoperative day and thereafter he had an uneventful convalescence. The fluid around the drains showed tryptic activity and continuous suction by a catheter was used. On the eleventh postoperative day bile appeared and the stools became clay-colored. Bile drainage ceased in five days. The wound healed well but there was intermittent pancreatic drainage for six weeks. He was discharged August 20, 1941.

Pathology Note.—The cut surface of the tumor measured 2×3 cm. in diameter. It obstructed both the common and pancreatic ducts to within 1 cm. of the ampulla, which was not involved. There was atrophy and fibrosis of the normal pancreatic tissue. Several lymph nodes examined showed no metastasis. *Pathologic Diagnosis.*—Adenocarcinoma of the head of the pancreas, Grade II.

Subsequent Course.—The patient returned to work one month after leaving the hospital, and has continued ever since. He has been on a regular diet, and continued to gain weight, now being rather obese and weighing 175 pounds. He has had no glycosuria, diarrhea or other evidence of disturbed fat or carbohydrate metabolism. *Roentgenologic Examination*, December 5, 1941, shows a normally functioning gastro-intestinal tract, with the gallbladder and biliary tree filled with air (Fig. 1). Liver shows no enlargement, March, 1942.

Comment.—This patient had a short history and was in excellent condition. In retrospect, it is likely that a one-stage procedure could have been done successfully. On the seventh postoperative day there was digestion of the wound evident. Bile did not appear until the eleventh postoperative day and lasted only five days. The pancreatic fistula drained for five weeks. Postoperatively, the patient followed a routine diet on which he gained weight, and there were no gross abnormalities of digestion noted. Occasionally during the first two months postoperatively he had a mild attack of diarrhea. The technical procedure would have been much easier in this patient if the intestine had been divided at the ligament of Treitz rather than in the third portion of the duodenum. The patient was fat and the mesentery to the small bowel thick. These factors, plus the location of the tumor adjacent to the third portion of the duodenum, rendered mobilization of this portion of the duodenum difficult.

Case 5.—*History No. 7023: A. C., female, age 53. Admitted May 18, 1941. Six months—constipation. Four months—itching. Three months—jaundice, pain, fatigue, clay-colored stools, 20 pounds' weight loss. Marked hepatomegaly. Cholecystogastrotomy. Refused second operation until three months later. Resection duodenum and pancreas, gastrojejunostomy. Operative death—acute yellow atrophy of liver.*

Chief Complaint.—Itching.

Present Illness.—In November, 1940, for the first time she became constipated and this persisted until the character of the stool changed in February, 1941. Early in January she developed itching over the entire body, worse on the extremities. She consulted different doctors and received various lotions and was once told she had scabies. She noted her skin was rather dark but it was not until February that it became yellow. At this time she became easily fatigued and lost her appetite. She shortly developed a sensation "as though the stomach were pressing on the back bone," food was disagreeable

and she frequently vomited. Epigastric pain appeared which was relieved by leaning forward. She also developed a lower abdominal cramping pain preceding bowel movements and relieved by them. She had lost 20 pounds' weight.

Past History.—Irrelevant except for hypertension of four years' duration.

Physical Examination.—The patient was a small, emaciated woman appearing chronically ill. Her skin was markedly jaundiced, having a peculiar dark bronze color, and there were numerous excoriations on the trunk and extremities. Tongue was heavily coated. The abdomen was slightly distended, the epigastrium very tender, and the liver enlarged to a hand's breadth below the costal margin.

Laboratory Data.—Blood: R.B.C. 4.2; hemoglobin 80 per cent; W.B.C. and smear normal. Urine: Negative except for strongly positive bile. Stool: Guaiac and bile negative. Serum proteins: 6.9 mg. per cent; serum albumin: 3.74 mg. per cent; serum globulin: 3.25 mg. per cent; icteric index: 95 units. Liver function test: 22.7 per cent sodium benzoate excreted in one hour as hippuric acid. Van den Bergh: qualitative direct negative; indirect, 8.75 mg. per cent. Gastric analysis: 4 cc. free HCl.

Roentgenograms negative except for displacement of stomach laterally and posteriorly because of questionable enlargement of liver.

Operation.—A.W.O.: June 2, 1941: Exploratory Celiotomy; Cholecystogastrostomy. The liver was found enlarged to the iliac crest and had a dark purple color, with a pebbled surface. The gallbladder and common duct were markedly dilated. There was a mass 3 cm. in diameter in the region of the common duct behind the second portion of the duodenum and in the pancreas. There was considerable edema and numerous dilated vessels. Some time was consumed in dissection and trying to decide whether this was a stone in the common duct or a tumor. An unsuccessful biopsy was attempted. Finally a cholecystogastrostomy was performed.

Postoperative Course.—Uneventful. The icteric index quickly fell to normal and the itching promptly ceased. The jaundice slowly faded, her appetite returned and symptoms disappeared. She felt so well that she refused further operative treatment and was discharged June 23, 1941. She continued to improve at home, gaining weight to 90 pounds. She had never weighed over 100 pounds. She wished to continue her dog farm during the profitable season but was finally persuaded to return to the hospital on August 24, 1941. In the meantime she had shown no free hydrochloric acid fasting but 16 units after histamine. Bromsulfalein liver function, 25 per cent dye retention in seven minutes, and no dye retention at 30 minutes. Icteric index 3.

Second Operation.—A.W.O.: August 28, 1941: Resection Duodenum and Pancreas; Gastrojejunostomy, posterior. An upper right rectus paramedian incision was made. The liver was still enlarged to four fingers below the costal margin. The tumor, instead of being smaller as in previous cases, had enlarged to 6 cm. in diameter. The first impression was that it was inoperable but as the dissection was begun it seemed that there was some possibility that it might be removed. The peritoneum was incised along the lateral surface of the duodenum which was turned up with the head of the pancreas. The right gastric and gastroduodenal vessels were ligated, the pylorus clamped and divided. The dissection was then carried along the inferior portion of the duodenum, entering the free peritoneal cavity at the ligament of Treitz. A specially devised curved clamp was then carried under the vessels of the mesentery. The transverse colon was then reflected upward, exposing the ligament of Treitz, and the clamp which was placed on the proximal jejunum. A Peyer clamp (Fig. 2) was placed just distal to this and the jejunum divided and inverted. The usual posterior gastrojejunostomy was performed. The dissection was then carried along the portal vein ligating the tributaries. The tumor was found tightly adherent to the wall of the portal vein, which at one point was entered but readily repaired. The remainder of the dissection proceeded without incident. The patient had had a stormy anesthesia and it was necessary to resort to drop-ether. However, she stood the operation quite well. At the completion her systolic blood pressure was 100-110, and pulse 90.

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Postoperative Course.—This patient never regained consciousness in spite of all supportive measures. She became rapidly and deeply jaundiced, and died within 48 hours. Sections of the liver showed typical acute yellow atrophy.

Comment.—There was undue delay in the diagnosis of this patient, and the primary liver damage was severe. A cholecystogastrostomy was performed at the first stage as being the simplest means of relieving the biliary obstruction in a critically ill patient. The optimal time for the second stage was missed owing to the patient's refusal. This situation, in itself, may be used as an argument for a one-stage procedure. When the second stage was attempted in this patient the tumor was larger than it was at the time of the

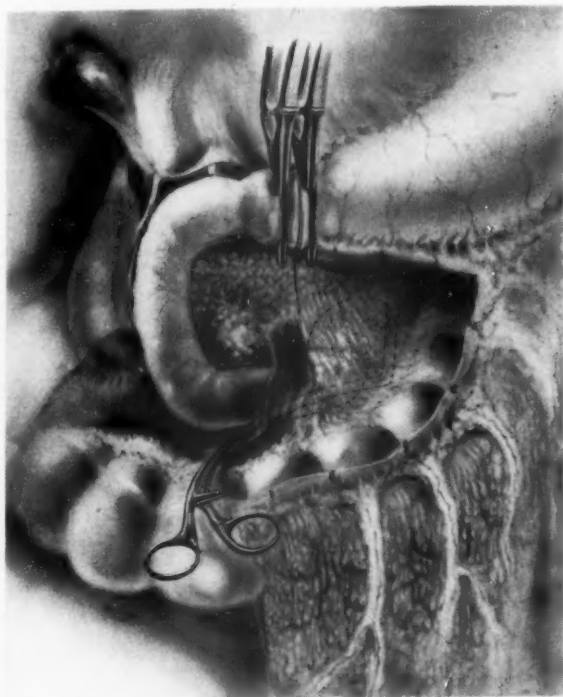


FIG. 2.—Case 5: A special clamp is used for division of the jejunum.

first operation, whereas in all the other two-stage procedures the tumor was smaller at the second operation than when seen at the first stage. In retrospect, this patient must also be considered as inoperable owing to extension of the tumor involving the portal vein, although this could not be determined without dissection of this area. Also, in retrospect, an unwise attempt was made to perform a radical removal of the tumor. She developed a typical syndrome of acute yellow atrophy of the liver, proven histologically. The cause of this is unknown but it is possible that a heavy ether anesthesia, in the presence of an already damaged liver, may have contributed to the fatal outcome.

Case 6.—History No. B17187: V. A., female, age 50. Admitted June 30, 1941. Three months—voluminous, frothy offensive stools; two months—anorexia and cramps preceding defecation; one month—red scaly eruption on hands and ankles, fissures at corner of mouth, 30 pounds' weight loss; five days—jaundice, glycosuria. One-stage resection duodenum and pancreas; cholecystojejunostomy; posterior gastro-enterostomy. Recovery. Diarrhea, diabetes and weakness persist but no evidence of recurrence. Avitaminosis. Still living nine months.

Chief Complaint.—Voluminous stools.

Present Illness.—Began three months before admission when one morning she passed a large malodorous, foamy, light-colored stool. During this morning she had three such stools and since that time she had had two to four similar bowel movements each day. Shortly after this she was placed on a bland diet without added vitamins and remained on this until admission. During this period she had had no pain except for a crampy generalized abdominal ache before defecation. Her appetite was poor and she had lost 30 pounds of weight. During the month preceding admission a dry, scaly, reddened eruption appeared on the dorsum of the hands and ankles and fissures developed about the corners of the mouth. She had never been jaundiced and stated that she did not have diabetes. *Past history and family history* irrelevant.

Physical Examination.—The patient was an emaciated woman, appearing chronically ill. There were scaly, erythematous, desquamating lesions on the ankles and dorsum of the hands. The corners of the mouth showed many fine fissures. The liver edge was palpable two fingers' breadth below the costal margin. A stony-hard 4 cm.-mass, which moved slightly with inspiration, was palpable in the right upper quadrant, just to the right of the midline.

Laboratory Data.—Blood: R.B.C. 3.7, hemoglobin 78 per cent. White count and smear normal. Urine: Albumin +, sugar 4+, acetone 2+. Stools were light greenish-brown, soft, semiformed, bile negative. Some specimens were guaiac positive and others negative. Icteric index: 8. Fasting blood sugar: 150 mg. per cent. N.P.N. 18 mg. per cent. Prothrombin time: 28 per cent of normal. Gastric analysis: Free HCl—65 units. After histamine, free HCl—76 units. Serum albumin: 3.95 gm. per cent; Serum globulin: 1.90 gm. per cent; Calcium: 9.91 gm. per cent; Phosphorus: 2.22 gm. per cent; Liver function (bromsulfalein 5 mg. per Kg.): 5 minutes—90 per cent retention; 30 minutes—60 per cent retention.

Roentgenologic Examination.—Gastro-intestinal series negative. Cholecystogram showed 50 per cent dye retention in 30 minutes, with nonvisualization of the gallbladder.

On the ninth day after admission she became jaundiced, the icteric index was then 35, and the direct Van den Bergh positive. During this preoperative period the patient was on a calculated diabetic diet containing protein 120 Gm., fat 50 Gm., with added calcium, viosterol and nicotinic acid. The insulin requirement varied from 20 to 50 units per day.

Operation.—S.C.H.: July 12, 1941: Retrocolic Cholecystojejunostomy; Posterior Gastrojejunostomy; Resection of Duodenum and Pancreas. An upper right rectus incision was made. The liver was normal in appearance but the gallbladder and common duct were markedly dilated. A hard, nodular mass, grossly carcinoma, was seen in the head of the pancreas. It was decided to perform the resection in stages in order that the operation might be terminated promptly if the patient's condition did not remain satisfactory. A retrocolic cholecystojejunostomy 40 cm. below the ligament of Treitz was carried out as a first stage. The pyloric end of the stomach was mobilized and divided and a posterior gastrojejunostomy was done, the proximal jejunum being utilized. In this manner the second stage of the operation was completed. The common duct was divided, ligated and transfixed with silk. The pancreaticoduodenal artery was ligated in continuity and divided. The first and second portions of the duodenum, together with the head of the pancreas, were then mobilized laterally; the pancreas was divided between clamps at the level of the superior mesenteric vein with preservation of the superior

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mesenteric vessels. The inferior pancreaticoduodenal artery and the pancreatic branches of the superior mesenteric vein were then ligated, following which the duodenum and tumor mass were retracted to the right and the duodenum divided just proximal to the ligament of Treitz. The entire duodenum and tumor mass were then removed *en bloc* and the distal duodenal stump closed. The remaining portion of the pancreas to the left of the superior mesenteric vessels was then resected well out to the tail, leaving about 2-3 cm. of attenuated pancreas. The wound was closed in the usual manner with interrupted silk. A slip drain was placed beneath the anterior rectus fascia but not into the peritoneal cavity.

Pathology Notes.—The tumor had completely closed the pancreatic duct but the common duct was still partially patent. Atrophic changes in the pancreatic tissue were marked. Diagnosis was adenocarcinoma of the head of the pancreas with secondary fibrosis and atrophy of the acini of the body and tail; metastases to the local lymph nodes.

Postoperative Course.—The patient made an uneventful recovery from the operation, the slip drain was removed in 48 hours, and the wound healed *per primam*, without evidence of a pancreatic fistula. The blood sugar on the morning of the first postoperative day was 126 mg. per cent. After the immediate postoperative period, and when peristalsis had returned, the patient was placed on a high protein, low fat, high carbohydrate diet with added vitamins, including vitamin K. Viosterol and calcium were given by mouth. The stools were dark brown, semiformal and guaiac negative, the prothrombin time normal. The bromsulfalein test (July 31, 1941) showed no retention at the end of 30 minutes. In the serum the titrated fatty acids were 8.0 mg. per cent per liter, the total cholesterol 123 mg. per cent, the unesterized cholesterol 40 mg. per cent, and the serum proteins 4.41 Gm. per cent. With the improvement in liver function there was a marked increase in the severity of the diabetes, and the insulin requirement was from 70 to 120 units per day. There were several episodes of diarrhea with bulky stools, which responded poorly to pancreatin by mouth. By the time a satisfactory lipocaic preparation could be obtained the patient was ready for discharge and this preparation was not given during her hospital stay. She was discharged from the hospital, August 16, 1941, 35 days after operation.

She was readmitted to the hospital, September 7, 1941, with a severe diabetes, acidosis and dehydration. Blood sugar was 329 mg. per cent. She was discharged, October 3, 1941, asymptomatic.

Since then there have been frequent attacks of diarrhea and steatorrhea, aggravation of the diabetes, some nausea and occasional vomiting. There have been marked weakness and a failure to regain the lost weight. A gastro-intestinal series has shown the gastrojejunostomy stoma to be patent. A bromsulfalein test (2 mg. per Kg. and, therefore, not comparable with the previous test) showed a 48 per cent retention of the dye at the end of 30 minutes. This was done December 30, 1941. The patient has subsequently shown evidence of multiple vitamin deficiencies and is at present in the hospital under treatment for this condition. The liver is readily felt and descends two to three fingers' breadth below the costal margin. This represents some enlargement since the pancreatectomy. On February 14, 1942, serum titrated fatty acids were 14.6 mg. per cent, and cholesterol 220 mg. per cent. Icteric index, March 20, 1942, increased to 40. The patient is now under treatment with lipocaic.

Comment.—This patient, in spite of a severe avitaminosis and diabetes, had an unusually smooth convalescence following a one-stage operation, without drainage. She did not have a pancreatic fistula, although only a very small amount of functioning pancreatic tissue remained. She is the only one of the six patients reported who presented the classical symptoms of voluminous, frothy, offensive stools usually associated with pancreatic deficiency. She is also the only one complicated by a severe and persistent diabetes.

She had, and still has, multiple vitamin deficiencies. It is not yet determined how much of her present difficulty is due to a food and vitamin deficiency and how much may be contributed by a lack of the external secretions of the pancreas.

DISCUSSION

Since cancer of the pancreas and ampullary region was fully discussed before this society last year by Hunt,⁵ Schnedorf and Orr,⁷ Whipple,⁹ and others, we will limit the discussion in this paper to points illustrated by the cases presented. Cancer of the pancreas and ampullary region may well be considered as an entity since it is frequently impossible clinically to determine the exact site of origin. Furthermore, the extension of strictly ampullary tumors makes it necessary for one dealing with this problem to be familiar with, and capable of executing, the radical excision of the duodenum and pancreas.

Reports on cancer of the pancreas are frequently pessimistic, and cite, as a basis for this pessimism, the short duration of symptoms and rapidly fatal course of the disease. It should be recalled, and history reveals, that this attitude prevails when cancer of an internal organ is first attacked therapeutically. Berk¹ has shown, in a review of the literature, that the average duration of symptoms from the onset of the disease to admission to the hospital is six months, with extremes of approximately four to ten months. This delay offers considerable hope that in the future, as the symptoms of the disease become more clearly recognized and the value of the radical surgery more definitely established, more optimism regarding cancer of the pancreas will be justified.

Symptoms. Berk¹ has recently surveyed the literature, with particular reference to symptoms and diagnosis. He states: "In many cases the disease is incorrectly diagnosed and its presence is missed in the early stages because in the mind of the average physician certain impressions of traditional diagnostic criteria have persisted despite the fact that they have been repeatedly shown to be false." He found, by a poll of recent graduates, that 92 per cent of them considered painless jaundice the most important symptom. On the contrary, a survey of the literature revealed that pain was one of the most common symptoms. Both as an initial symptom and as a chief complaint, it was found in approximately half the cases, whereas sometime during the course of the disease pain was found in 76 per cent of all patients.

The type of pain cannot be said to be characteristic (Cases 1, 2, 3, 4 and 5). Pain such as is illustrated in Case 1 is most characteristic. It is severe, and frequently described as though the stomach were pressing on the back bone, and is worse on reclining. It is frequently relieved by relaxing the abdomen or standing up.

Jaundice, as an initial symptom or chief complaint, is less frequent than pain (Cases 1, 3, 4, and 6). It is obvious that the location and extent of the tumor determine the symptoms. Since the cancer is located in the head of the

pancreas in 92 per cent of the patients who came to operation and in 72 per cent of those at necropsy, jaundice sometime during the course of the disease is a common symptom. Either the common or pancreatic duct or both may be involved. Even when the cancer arises in the ampulla, one or the other of these ducts may remain patent. In Case 2 the tumor of the ampulla completely blocked the common duct, whereas the pancreatic duct remained patent. Brunschwig reported a similar tumor the same year, treated in the same manner, in which only the pancreatic duct was blocked. It should be emphasized that while painless jaundice should lead one to suspect cancer of the head of the pancreas, this syndrome is found in only 18 per cent of all patients with such tumors. It was found in only one patient in this series.

A palpable liver or gallbladder is frequently cited as of diagnostic significance. The enlargement of these organs appears to depend chiefly on the degree and duration of the obstruction of the common duct. An enlarged liver is more frequently noted than an enlarged gallbladder. Considering all the cases with jaundice in the literature, only half have had a palpable gallbladder. Even though the common duct is completely obstructed, with jaundice present, but for a short time (Cases 2 and 4), the liver and gallbladder may not have had time to enlarge.

Weight loss is frequently profound and rapid. Berk found it to average 26 pounds, or 6.8 pounds per week, and it was present in 87 per cent of all patients. Fatigue and weakness, as well as nausea or vomiting, are also frequent symptoms. Carcinoma of the pancreas is frequently thought to be associated with voluminous, foul, frothy diarrhea. This is not a frequent occurrence, and was found in only one of the six cases reported. Berk¹ found diarrhea reported in only 11 per cent of the cases in the literature. It is not clear why some patients have the typical fatty diarrheal stool and others, with a similar lesion, have no obvious abnormality of fat metabolism. The one patient in this series (Case 6) who manifested such a diarrhea also had a severe avitaminosis. She also had less functional pancreatic tissue remaining.

Laboratory Data.—The roentgenographic findings are variable and frequently disappointing, particularly when the tumor is still in the operable stage. Positive roentgenographic findings are reported in the literature of 37 per cent of all cases. However, many of these were inoperable. Roentgenograms may demonstrate: (1) Obstruction of the duodenum; (2) irregularity or encroachment on the duodenum; or (3) widening of the duodenal loop. Occasionally a large tumor of the tail or body of the pancreas may be seen pressing on the stomach. A negative roentgenogram has no significance in the diagnosis of cancer of the pancreas or ampullary region (Cases 1, 2, 4 and 6).

Laboratory findings are variable in the presence of carcinoma of the pancreas. Disturbances of fat and carbohydrate metabolism might be expected, depending on the location, extent and duration of the tumor.

Glycosuria has been reported in the literature in 10 per cent of all patients

with cancer of the pancreas. In different reports the frequency of this finding varies from 2 to 26 per cent. Likewise, hyperglycemia was found in 20 per cent of all patients, with a spread of 9 to 57 per cent in different reports. The more recent reports have a tendency to recognize a higher incidence of disturbed carbohydrate metabolism, probably because of more and better laboratory work. The glucose tolerance test presents a similar variability. Ranson, in 1935, found an impaired glucose tolerance in only one of 16 cases (6.2 per cent) whereas Berk found seven of nine patients (77.8 per cent) showed a positive test. The glucose tolerance test appears to be indicated in all suspected cases, since it has yielded valuable information when neither glycosuria nor hyperglycemia has been present.

In this series, Case 1 gave a history of glycosuria. However, on admission his fasting blood sugar was 79 mg. per cent and a few days later it was 130 mg. per cent. He showed no glycosuria while in the hospital. After 50 Gm. of glucose his blood sugar rose to a high of 128 mg. per cent in two hours. After a subtotal resection of his pancreas, leaving only a small ribbon 1 cm. wide on the head of the pancreas along the duodenum, he still did not show glycosuria. Case 6 showed a persistent 4+ glycosuria unless controlled by insulin or diet. Preoperative fasting blood sugar was 159 mg. per cent. Following operation the glycosuria fluctuated according to the diarrhea, being less when the diarrhea was greatest. On one occasion, following operation, she was admitted to the hospital with severe diabetes, acidosis and dehydration. None of the other patients gave evidence of disturbed carbohydrate metabolism.

There are a number of experimental observations which may be cited to explain the variable response of depancreatized patients. It is well known that pancreatectomy in different species of animals results in different degrees of disturbed carbohydrate metabolism. There is evidence that this is in part due to the different activity of the pituitary and adrenal glands. In man the high incidence of glycosuria in acromegalic persons is circumstantial evidence. Thus, as stated by Best: "The diabetic state, therefore, may not be due primarily to subnormal secretion of antidiabetic hormone but to various other hormonal disturbances, especially of the pituitary and adrenals." It may be added that the thyroid also plays an indirect rôle. In support of this we may cite one patient who was suffering from acromegaly, hyperthyroidism and severe diabetes. Following thyroidectomy the patient's previously high insulin requirement was reduced to a low level. It is also possible that the part of the pancreas removed may be a determining factor. It is known that in the dog different parts of the pancreas contain different amounts of the antidiabetic factor (splenic end 4, middle 3, and duodenal end 2 units per Gm.). A history of preceding diabetes or a family history of diabetes may be obtained, as in Case 4. McKettrick and Root found carcinoma of the pancreas comprised 32.4 per cent of all malignant conditions with a history of diabetes. Others have maintained that a preceding history of diabetes is incidental.

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The evidence for deranged fat metabolism also presents a similar variability. There are now a number of living patients who have survived a subtotal pancreatectomy, and who have had no obvious evidence of disturbed fat metabolism. In some of these patients there seems to be no doubt that the external secretions of the pancreas do not reach the intestines. One may, therefore, infer that the external secretions of the pancreas are not essential to life or that their functions may be taken over by other portions of the gastro-intestinal tract in some patients.

Various methods of determining faulty fat metabolism in cancer of the pancreas have been tried but the results have usually been disappointing. This may have been due to the fact that cancer of this organ does not produce a constant clinical syndrome nor result in uniform pathologic changes in the pancreas. Serum lipase determinations appear to hold considerable promise as a diagnostic test. Various authors have found that the serum lipase is elevated in a high percentage of cases of pancreatitis. However, Comfort and Osterberg found increased values in only 40.5 per cent of 69 cases of carcinoma of the pancreas. One may conclude that the absence of evidence indicating disturbed fat metabolism is of no significance in the diagnosis of cancer of the pancreas. However, a search should be made for evidence of disturbed carbohydrate or fat metabolism as its presence in conjunction with other findings may be of help.

Surgical Treatment.—The preoperative treatment of patients with cancer of the pancreas involves the same principles as does cancer of the stomach or extrahepatic bile ducts. An attempt should be made to restore the physiology of the patient to as nearly normal as possible. The causes of death, as recorded by Hunt, in operations for periampullary cancer, in the order of frequency, are hemorrhage, peritonitis, duodenal fistula, shock and pneumonia. Most of these problems have been solved by the use of vitamin K in the jaundiced patient, hydrochloric acid for the infected stomach with low acidity, improved surgical technic, adequate use of intravenous fluids, blood and plasma, the use of chemotherapy, adequate parenteral vitamins, and improved anesthesia. With these considerations in mind, there is already reason to suppose that the operative mortality in experienced hands will not exceed 10 to 15 per cent.

The technic of the operation, whether it shall be local or radical, one-stage or two-stage, and the treatment of the bile and pancreatic ducts, has been not yet clearly established. The more formidable radical operation for cancer of the ampulla has been frequently avoided in the past. Several of these patients, reported in the literature, having a local excision have had a recurrence. It is reasonable to suppose that in some of these a more radical excision might have resulted in a cure. Case 2 is a successful result to date (two years, nine months), but a local operation of this type cannot be considered an ideal operation for cancer, and the surgeon who approaches one of these tumors should be prepared to perform the radical operation if indicated.

The advantages of the one- and two-stage operations have been discussed

by Whipple. Evidence is accumulating that the one-stage operation may be the procedure of choice. The operative mortality of the one- and two-stage operation, as reported, is about equal, although the numbers reported appear to be too few to enable one to draw final conclusions. There are undoubted and obvious advantages in a radical removal of the tumor at one operation, and it is to be hoped that this will be possible as more patients are diagnosed in the earlier and more favorable stages of the disease. However, it is likely that a two-stage operation may still be indicated in some patients, and the problem is raised as to when this is necessary. If the cancer is localized in the tail of the pancreas and removal of the duodenum is unnecessary, there is no indication for a two-stage operation (Case 1). There is also no indication for a two-stage operation in the rare patient with a small cancer of the ampulla which can be excised with an adequate margin and the ducts reimplanted (Case 2). The radical excision of the duodenum and pancreas with a cholecystojejunostomy and gastrojejunostomy, would not seem to be contraindicated if the liver has not been seriously damaged and the patient is in otherwise good condition. In retrospect, it would seem as though Case 4 might have been safely concluded in one operation rather than two. However, it is frequently difficult to determine before operation how well a patient will stand such a long and arduous procedure (Cases 3, 5 and 6). The operation described in Case 6 illustrates a method whereby the procedure may be terminated at any of three stages if the patient is not doing well, or it may be completed in one operation as in this case. One of the chief disadvantages of the two-stage operation is illustrated by Case 5. The long-standing jaundice and evident liver damage appeared to indicate the advantage of a two-stage operation. Furthermore, considerable time had been consumed in an effort to determine whether the patient had a cancer or a common duct stone. She withstood the procedure well, under cyclopropane anesthesia, and it is likely she would have withstood a radical excision equally well. Following this she felt so well that she refused the second operation until nearly three months later. She then appeared to be in much better general condition. However, she took a poor anesthesia, requiring drop-ether, the tumor had increased in size, and was followed by acute yellow atrophy of the liver, and a fatality.

Biliary and pancreatic fistulae have been one of the annoying complications of operations for cancer of the pancreas. Two patients in this series had biliary and pancreatic fistulae, and both were two-stage operations (Cases 3 and 4). In both patients the biliary fistula appeared several days after the pancreatic secretions appeared. The pancreatic secretions possessed marked tryptic activity, suggesting that this may have been a factor in digesting the common duct closure. In both patients the common duct was ligated with silk at the second operation. It is possible that the biliary fistulae could have been avoided by ligation and division of the common duct at the first operation, before the pancreatic secretions were freed. Both of these patients had drains placed to the cut surface of the pancreas. Since the one-stage

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operations (Cases 1 and 6) were not drained, one might assume that this was responsible for the fistulae. However, both of these patients had little indication for drainage since, in Case 1, the ducts draining the remaining pancreas were still intact, and in Case 6, only a very small amount of the atrophic tail of the pancreas remained. In Cases 3 and 4 the ducts were filled with secretion at the time of operation and more secreting pancreas remained *in situ*.

Some surgeons have anastomosed the jejunum to the common duct, which may be preferable to the cholecystojejunostomy. Leakage from the ligated common duct might thus be avoided. The cholecystogastrostomy appears to have fallen into disrepute owing to constriction of the stoma and the fact that it is frequently followed by subsequent liver damage. Data is not available as to whether this liver damage may occur only in those patients with an infected gastric content owing to absence of hydrochloric acid. It is worthy of note that all patients with a cholecystojejunostomy have shown air throughout the biliary tree, indicating the possibility of ascending infection by this route likewise.

TABLE I
RÉSUMÉ OF CLINICAL DATA

Case	1	2	3	4	5	6	Average in Literature*
Pain.....	+	0	+	+	+	0	50†-76%
Jaundice.....	0	+	+	+	+	0	22†-69%
Pounds' weight loss.....	15	26	20	10	20	30	87% Av. 26 lbs.
Fatigue and weakness....	+	+	+	+	+	+	51%
Nausea or vom- iting.....	+	0	+	+	+	+	42%
Diarrhea.....	0	0	0	0	0	+	11%
Glycosuria....	+	0	0	0	0	+	10%
Location of tumor.....	Body	Ampulla	Head	Head	Head	Head and body	82% of all cases in head
Operation.....	Resection spleen and pan. only	Resection tumor, trans- duodenal	Resection duod.and pan. 2 stages	Resection duod.and pan. 2 stages	Resection duod.and pan. 2 stages	Resection duod.and pan. 1 stage	
Results.....	Died 5 mos. postop., with met- astasis	Living and well, 2 yrs. and 8 mos.	Died sud- denly, 3 mos. postop.	Living and well, 9 mos.	Op. death, acute yel- low atrophy	Living, 9 mos.	

* Berk, J. Edward¹.

† Initial symptom only.

The postoperative care of patients following a radical resection of the pancreas is not clearly established. It appears that only a very small amount of pancreas is necessary to prevent diabetes. It appeared in only one patient in this series, and was present before operation (Case 6). It also appears that in some patients the external secretions of the pancreas are not essential to life. If further experience should prove that the external secretions are essential in some patients, then some satisfactory method of anastomosing

the pancreatic ducts to the intestine must be developed. More observations and a careful follow-up will be needed to determine whether such changes as a fatty infiltration of the liver will occur. The nature of lipocaic and how it prevents fatty infiltration of the liver is not clear. Recent observations indicate that lipocaic, pancreas, rice polishings and yeast contain a dietary factor which prevents this liver damage. Hence, it may be found that a patient with a normal liver and an adequate diet may require no supplementary therapy (Case 4). It appears that most of the known enzymatic functions of the external secretions of the pancreas may be performed to a greater or less extent by some other portion of the gastro-intestinal tract.

SUMMARY AND CONCLUSION

(1) Six patients with cancer of the pancreas and ampullary region are reported.

(2) There was one local excision of cancer of the ampullary region and five radical operations, with one fatality (16.6 per cent).

(3) There were four radical excisions of the duodenum and pancreas.

(4) Three of the six patients are still living, one of whom has symptoms of disturbed carbohydrate and fat metabolism.

(5) The external secretions of the pancreas in some patients do not appear to be essential to life.

(6) Earlier diagnosis of more patients with cancer of the pancreas, still in the operable stage, is possible. The radical excision of the tumor is also possible, with a comparatively low mortality. More observations and follow-up reports on patients having these operations are needed.

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DISCUSSION.—DR. ALLEN O. WHIPPLE (New York, N. Y.): The remarks that Doctor Churchill made this morning in regard to the radical procedures for carcinoma of the lower end of the esophagus and of the cardia, apply very aptly to this operation for carcinoma of the pancreas in the ampullary region of the duodenum. The operation is unquestionably in an experimental stage. That is obvious from the study of the cases that have been reported recently.

Doctor Harvey and Doctor Oughterson were among the members of this society who very kindly sent to me the reports of their cases, and I wish to express my appreciation to the members of the Association for this courtesy, whether they were published or not. I certainly would appreciate others doing so.

During the past year some 23 radical operations with removal of the duodenum and the head, or more of the pancreas, have been reported in the literature or have been reported to me by surgeons here and abroad, bringing the total number of these operations since 1935 to 64. As a result of the introduction of three factors, vitamin K, the newer methods of preventing and combating shock, and the sulfonamide compounds, there is a very definite and fully justified trend toward the one-stage operation, as shown in increasing statistics.

TABLE I
RÉSUMÉ OF 64 CASES OF RADICAL PANCREATICODUODENECTOMY OPERATIONS
Collected to April 1, 1942

	Two-Stage	Postop. Deaths	One-Stage	Postop. Deaths	Fistulae		
					D.	B.	P.
Carcinoma of the ampulla.....	15	2	6	2	—	6	8
Carcinoma of the pancreas.....	21	9	6	2	2	5	5
Carcinoma of the duodenum.....	2	1	7	2	—	—	2
Carcinoma of the common duct.....	3	0	2	2	—	1	2
Sarcoma of the duodenum.....	0	0	1	0	—	—	—
Chronic pancreatitis.....	0	0	1	0	—	—	1
Totals.....	41	12	23	8	2	12	18
Total operated cases.....	64						
Postoperative deaths.....	20						
	Two-stage	12	29.2%				
	One-stage	8	34.7%				

From my own experience, I am convinced that the one-stage operation, aside from saving the patient two anesthetics, two operations, and very often a very unfortunate delay between the first and second stage, as Doctor Oughterson mentioned, avoids the risk, or largely decreases the risk, of the biliary fistula from ligation of the cut end of the common duct by the immediate anastomosis of the common duct to the loop of duodenum.

This is a real advance in the technic and result of the operation.

Dr. Herman Pearse has recently used the distal jejunal end to anastomose the gall-bladder proximal to gastrogastrostomy.

About a month ago I carried out a very extensive one-stage resection of the antrum of the stomach, all of the duodenum, and to some extent the jejunum, together with all the head of the pancreas, uniting the cut end of the jejunum to the cut end of the common duct, approximately to the site of gastrogastrostomy. This patient *did* develop a pancreatic fistula, but that is now closing.

The problem of what to do with the stump of the pancreas is still unsolved. I have performed a pancreaticoduodenostomy, in which the distal end of the pancreas was implanted into the distal portion of the duodenum in two patients, according to the scheme as first carried out by Koch in 1912. One of these patients has done exceedingly well, but the other patient developed a duodenal fistula, and on the tenth day had a very severe secondary hemorrhage which resulted in his death.

We do not know as yet how essential the external secretion of the pancreas is in the metabolism of fat and its relation to fatty changes in the liver. We have observed three patients who have gone two years or more after total exclusion of pancreatic juice from the tract. Two of these patients were able to digest 80 to 85 per cent of manufactured

FIG. 1 A.

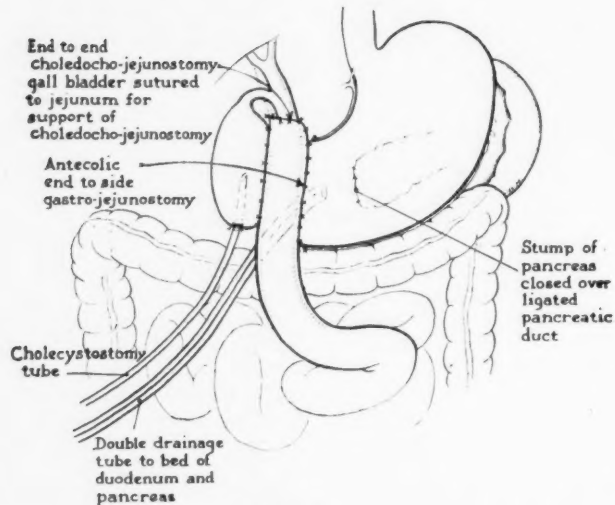
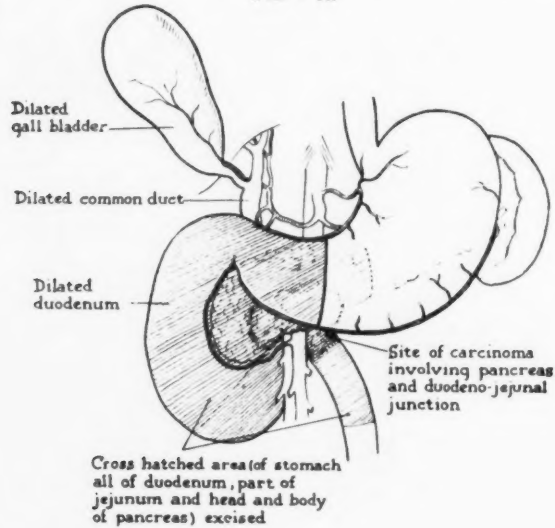


FIG. 1 B.

fat intake, whereas one has shown 40 per cent fat residue in the stools. I think the reason for that is because we removed so much of the pancreas, very much as in the case Doctor Oughterson reported. I believe that Doctor Dragstedt will be able shortly to give a definite opinion on this controversial question.

(Slide) This is a résumé of the total number of cases reported in the literature or reported to me, with a mortality of 12 or 29.2 per cent in two-stage procedures, and a mortality of 8, or 34.7 per cent, in one-stage procedures.

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In my own case I have carried out four two-stage operations, with two deaths, and six one-stage operations with four deaths.

(Slide) This was an extensive removal of the stomach, of the duodenum, and a large carcinoma of the jejunum. This is the patient in whom I transplanted the head of the pancreas into the stump of the duodenum.

(Slide) This is the antrum of the stomach, pylorus and all the duodenum and some ten or 12 cm. of the jejunum with the head of the pancreas.

(Slide) This shows the amount of tissue removed, the tumor being located here. The next slide shows the procedure which we carried out and which saved an inversion, brought the jejunum just to the point where it was resected, anastomosed the stomach, and implanted at the upper end the stump of the common duct. That patient has not had a biliary fistula and has done better than the average. I placed a tube in the gallbladder because it seemed to be rather tender and dilated.

I again wish to state that the procedure is in the experimental stage and that, like the operations that Doctor Churchill discussed this morning, it requires a great deal of further study and follow-up.

DR. THOMAS C. ORR (Kansas City, Kans.): Two patients reported earlier are still living 23 months and 12 months following the operation. Both were operated

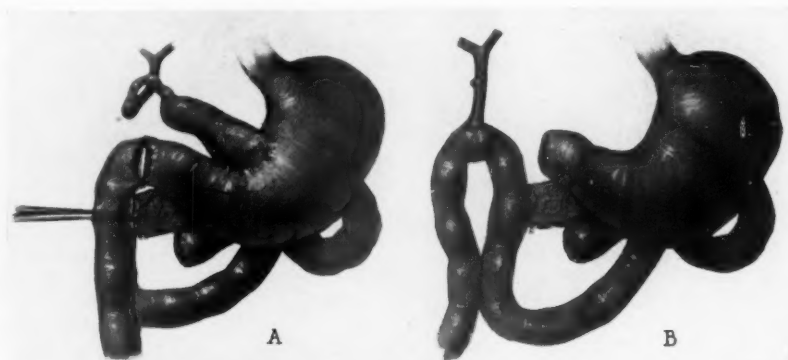


FIG. 1.—(A) Case 1: Two-stage operation. Cholecystogastrostomy followed in 117 days by resection of the head of the pancreas. Neck of pancreas anastomosed to jejunum. (B) Case 2: One-stage operation. Pancreas and common bile duct anastomosed to a jejunal loop.

upon by the method described by Whipple, Parsons, and Mullins. The following two cases have not previously been reported.

Case 1.—Female, age 65, was operated upon for carcinoma of the head of the pancreas in two stages. A cholecystogastrostomy was done September 11, 1941, and the duodenum and head of the pancreas were resected January 6, 1942. The stump of the pancreas was anastomosed to the jejunum (Fig. 1 A). The abdominal wound healed promptly after the second operation and the patient left the hospital in 14 days. The pathologist's diagnosis was "early adenocarcinoma of the pancreas arising from the ductal structures." At present, April 1, 1942, her condition is satisfactory.

Case 2.—Male, age 56. On April 28, 1939, the gallbladder was removed and the common duct was drained. There were no stones found in either the gallbladder or common duct. An obstruction of the common duct developed in November, 1941. The head of the pancreas and duodenum were resected in one stage, December 24, 1941. The severed end of the pancreas was anastomosed to the jejunum (Fig. 1 B). There was some serous discharge from the wound but no evidence of pancreatic secretion. He left the hospital in 31 days. The pathologist reported a "large ulcerating adenocarcinoma of the head of the pancreas with metastases to the regional lymph nodes; tumor probably arose from the parenchyma of the pancreas." A report received April 1, 1942, states that his condition is very good.

DR. J. SHELTON HORSLEY (Richmond, Va.): The physiologists, Doctor Whipple, and Doctor Brunschwig, and others, have shown, very definitely, that the external secretion of the pancreas through the pancreatic duct is not necessary to life. However, like the old jingle that poverty is no disgrace, it certainly might be claimed that it is sometimes inconvenient. The methods of making these observations are probably not entirely fully settled, and it certainly is convenient to have the external secretion preserved if it can be accomplished. Of course, in most instances the lesions are so extensive that this cannot be done.

(Slide) I want to again report one case that has been reported previously. It is a case that I have mulled through because the diagnosis was not accurate preoperatively. That patient is still dead, so I cannot have an excuse for reporting my own progress. He was a man, about 60 years of age, who was in good health, but about two months before entering the hospital he had jaundice. The jaundice increased. He had two very severe attacks of pain and apparently gallbladder involvement. When he entered the hospital his icteric index was upward to 150. After preliminary treatment I operated upon him, expecting to find probably a stone in the end of the common duct, though his icteric index was quite high. I found instead the gallbladder thickened and adherent. It was opened and a whitish material was evacuated, but in the head of the pancreas was a small infiltrating mass which involved the wall of the duodenum. The duodenum was somewhat contracted, so I thought it was probably an early cancer and I excised it. This is the specimen after its removal, showing the duodenum, the common duct, and the pancreatic duct. (Slide) This is the inside of it. (Slide) The adenoma was not cancer. It was fibroadenoma, with considerable infiltration, but definitely not cancer.

(Slide) This is the technic that I employed in that case. I had already opened the gallbladder, and I had no particular difficulty in excising the duodenum, together with a small portion of the infiltrated head of the pancreas. This proved later to be inflammatory and not very extensive, so I brought up this distal end of the duodenum and attached it to the greatly dilated end of the common duct with silk sutures. Then I did the same anteriorly, and put in another row of sutures at the pancreatic duct, put in another row of silk sutures and over that sutures of fine catgut, which brought up the duodenum, pulled it over the raw surface of the head of the pancreas, and attached it all around to a margin of the pancreatic stomach. In addition, we brought up the fatty tissue omentum and sutured that.

The patient made a very satisfactory operative recovery. He left the table with a pulse of only 88, and in 36 hours he was still doing well. Then he developed symptoms of uremia, passed no urine, and died on the fifth day.

At necropsy, I found the abdomen was in very good condition. The kidney showed evidence of nephritis. It was hypostatic pneumonia. While the patient died, it looks as though there might be a very limited field for that type of operation in which not much of the pancreas has to be excised.

May I say in connection with these types of operations, the one that Doctor Orr showed and the one of Doctor Brunschwig's, in which a loop of duodenum is brought up and attached to the gallbladder, that lateral anastomosis between these loops can be made very easily with a little rubber band that I mentioned yesterday. This band can be inserted quickly. It does not open the lumen of the bowel, and it has in no way any originality in the way of elastic ligature, which McGraw established years ago. It is merely another application of a principle that he established. Resenia, for instance, established the principle of using silk, and the procedure of Doctor Wangensteen, of course, is based on the principle established by Doctor Maddock.

DR. LESTER R. DRAGSTEDT (Chicago, Ill.): In 1939, I presented a report before this Association on the significance of lipocaic in surgery, indicating that a field of usefulness for this substance might appear with the further development of pancreatoduodenectomy in the treatment of cancer of the ampulla and head of the pancreas. At that time there was still some dissent to our conclusion that lipocaic is an internal secretion of the pancreas, distinct from insulin, which is necessary for normal nutrition and life. At present I believe all are agreed that the beneficial effect of the oral administration of whole pancreas or of fat-free alcohol extracts of pancreas in preserving the life of insulin-treated depancreatized dogs and in preventing the usual fatty infiltration of the liver in such

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animals cannot be accounted for on the basis of lecithin, choline, betaine, or the general lipotropic action of protein. In a report at the recent meeting of the American Physiological Society we have also presented evidence indicating that inositol is not the active principle of lipocaic. There seems no reason to doubt that lipocaic is a specific substance, probably protein in nature, manufactured by and present in the pancreas, which is necessary for life and for the normal transport and utilization of fat.

While adequate data are not yet available, it seems likely that following complete pancreatectomy in man both insulin and lipocaic will be required. The situation resulting from excision of the head of the pancreas and adjacent duodenum is more obscure. In this case pancreatic juice fails to reach the duodenum and more or less extensive degeneration of the pancreas results from the occlusion of the ducts. The absence of pancreatic juice may be expected to produce some impairment in the digestion and absorption of fat. Doctor Vermenlen, in our laboratory, has recently found that the depancreatized dog absorbs only 70 per cent of the food fat, whereas in the normal animal absorption is practically complete. This defect in digestion and absorption of fat is not corrected by lipocaic and is little influenced by the administration of pancreatin or pancreatic juice. It should be emphasized that there is at present no evidence that lipocaic affects the digestion or absorption of fat under any conditions. The development of fatty infiltration of the liver and the other sequelae of lipocaic deficiency following occlusion of the pancreatic ducts in the dog, depends apparently on the extent of pancreatic degeneration that follows this procedure. Of 19 animals, in our laboratory, in which this operation was done, only four developed fatty livers. Doctor Brunschwig excised the head of the pancreas and ligated the ducts in two monkeys. Neither of these developed a fatty liver. I recently excised the head of the pancreas and adjacent duodenum in a man for carcinoma of the ampulla and common bile duct. This man survived for four months, and at death the liver contained no excess fat, although the pancreatic ducts were found to be obstructed, markedly dilated, and the pancreas degenerated. However, until a good deal more data on man become available it would seem wise to watch these patients carefully for evidence of developing lipocaic deficiency. This may be manifested by progressive loss of weight and strength, hepatomegalia, and impaired liver function as revealed by the bromsulphalein excretion and hippuric acid synthesis tests. Profound alterations in the concentration of blood lipids may be found. In dogs with lipocaic deficiency, the blood lipids are usually reduced to approximately one-half the normal values. In man, however, we have seen a number of cases of hypercholesterolemia, hyperlipemia, hepatomegalia, and xanthomatosis, where the administration of lipocaic has brought about a dramatic chemical improvement and return of the abnormal blood chemistry toward normal levels. Lipocaic deficiency in man may, therefore, in some instances be indicated by increase rather than decrease in the lipid constituent of the blood.

DR. VERNE C. HUNT (Los Angeles, Calif.): Since reporting before this Association, a year ago, four cases of ampullary carcinoma that we had operated upon successfully, I have had occasion to operate upon another similar case, in which I performed a modification of the so-called Whipple radical operation, which makes a total of five cases of ampullary carcinoma that we have successfully operated upon without surgical mortality.

The first two of these, as some of you will recall, were by transduodenal excision, and the last three by resection of the duodenum and the head of the pancreas. These were done as one-stage, if one is willing to accept as one-stage operation the procedure of the resection of the duodenum, duodenectomy, and resection of the head of the pancreas.

All of these five cases occurred in our private surgical practice. I speak of that for two reasons. First of all, it is indicative to me that this lesion is not as uncommon as we are led to believe, when there are that number of cases in a small private surgical practice. I speak of this also because of the fact that these five patients were subjected to an early surgical viewpoint, in contradistinction to what I believe is true in many Services, particularly in Medical Services, where many of these patients come in and are placed on the medical wards, where they are subjected to prolonged and repeated differential diagnostic séances, so to speak. The point I want to make is that there is just one way to make diagnosis of this lesion, and that is on surgical exploration.

I have about taken the position that no patient with obstructive jaundice should be allowed to die without surgical aid. I mean that both ways. There are some patients

who may die following surgical exploration. However, I would much rather have them die following a surgical exploration for an inoperable lesion, than die a medical death with no opportunity for surgical exploration. There are few internists and medical men who are aware of the fact that surgery has possibilities in this area.

(Slide) This patient was operated upon last October, in whom we performed a one-stage resection, total duodenectomy, and resection of the head of the pancreas.

(Slide) We performed the operation of resection of the head of the pancreas at the open end of the duodenum. This shows a slide of the pancreas removed, and I think you see the well demarcated scar.

(Slide) You will be interested in the results of these patients. This is Case 4 that I reported a year ago. I bring it back to you again to refresh your memory and show you there is retroperitoneal lymph node involvement. This patient is living and clinically well, 13 months following operation. I might say that of the five patients we have operated upon, four of them are living. The first one with transduodenal resection, that I reported a year ago, is living nearly three years, with retroperitoneal metastasis no longer present. At least the patient is subjectively well, and we have no grounds to-day to believe that the patient has metastasis. We have another one living following the radical operation of two years and one month, and this one, one year and one month, and the last case, seven months.

(Slide) I wish to show this slide for two reasons. Whatever the facts may be regarding the value of preserving pancreatic secretion (external pancreatic secretion), I was very much interested in what Doctor Dragstedt had to say. As you all probably know, who are interested in this field of surgery, the observations and conclusions of Doctor Dragstedt, and of Doctor Montgomery, in San Francisco, are quite at variance regarding the effect of the external secretion of the pancreas on lipid metabolism. Whatever subsequent events may prove to be the fact, I believe it is still paramount, whenever it is possible, to preserve pancreatic secretion, and I think in many instances it can be done.

DR. HERMAN E. PEARSE, JR. (Rochester, N. Y.): Doctor Whipple has mentioned that I suggested the use of the end of the jejunum to anastomose to the biliary tract. I did this because I excised all the duodenum.

I wish to say one word about this. As the scope of the operation is enlarged to remove all of the head and the uncinate process of the pancreas, one may interfere with the circulation of the distal duodenum. Recently, I lost a case because I did not include the duodenum when I made such an excision. The patient died, and at necropsy the stump of the duodenum that I had allowed to remain had become necrotic and peritonitis developed from the breakdown of the suture.

DR. ASHLEY W. OUGHTERSON (closing): There was so much interest expressed in this subject and the subject was so well covered that I have little more to add.

In the first place, I would like to say that there are many studies which I did not have time to go into in relation to liver function, fats, etc., but several of our patients did have a very markedly diminished liver function, which seemed at least to warrant a two-stage procedure in order to give additional safety. And I must say Doctor Harvey is rather on the other side.

In regard to the indispensability of the external secretion, perhaps nine months of the year is a short time to regard that as being finally solved, but certainly for that period some of these patients at least get along on a normal diet without any difficulty.

In regard to typical fatty stools and the use of pancreatin and lipocain, on the one patient it had no influence.

It is also worthy of note that this is the only patient who had a severe avitaminosis preceding the operation and the same avitaminosis afterward, which so far they have been unable to correct.

POSTOPERATIVE NITROGEN LOSS AND STUDIES ON PARENTERAL NITROGEN NUTRITION BY MEANS OF CASEIN DIGEST*

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THE NITROGEN METABOLISM of the surgical patient has been the subject of special consideration in recent years. The possibility of parenteral administration of nitrogenous foodstuff further extends the practical aspects of this problem.

A major surgical procedure with operative manipulation of deeply situated viscera and tissues followed by a brief period of starvation and then gradual return, over several days, to ingestion of normal diet constitutes together with the complications often developing, such as shock, fever, vomiting, the presence of injured tissues, *etc.*, an altered physiologic state. Because intake of nitrogen obviously does not equal output during this period, a state of negative nitrogen balance exists for varying periods. Operative trauma itself may be the cause of increased nitrogen catabolism (so-called toxic (?) destruction of protein.)

In order to obtain some concrete conception of the extent of this loss, in 41 patients subjected to major operations of various types, nitrogen balance studies were carried out from the day of operation to and including the tenth postoperative day.

Urine, feces, excess sputum, biliary or other drainage, vomitus and gastric aspirations were collected each 24-hour period and analyzed for nitrogen (Micro-Kjeldahl), and this was compared with the nitrogen intake each day. The latter was obtained from standard dietitians' charts and this portion of the data represents, therefore, an approximation, since it was not practical to analyze each sample of food received from day to day for the exact nitrogen content.

The conditions pertaining to the postoperative management in this group of patients were: (a) Where the abdomen or thorax was not opened liquids were permitted by mouth as soon as tolerated and shortly thereafter a soft or regular diet was given, the latter being taken by the third to fifth postoperative day; and (b) where the abdomen or thorax was opened nothing was taken by mouth for the first 48 to 72 hours, fluids being given parenterally; on the third or fourth day small quantities of water were taken at hourly intervals, the next day clear liquids, and if tolerated soft to regular diet ingested by the sixth or seventh day, except in operations upon the stomach, where increase in food by mouth was more gradual.

* This work was conducted under a grant from the Mead-Johnson and Company, Evansville, Ind.

* Read before the American Surgical Association, Cleveland, Ohio, April 6-8, 1942.

Blood transfusions which were given in many cases following operation have not been taken into account in calculating the nitrogen balance.

The results of the studies on net nitrogen loss (or gain) over the ten-day postoperative period are shown in Table I.

TABLE I
NET LOSS OR GAIN IN NITROGEN IN TEN-DAY POSTOPERATIVE PERIOD IN 41 PATIENTS
UNDERGOING A VARIETY OF MAJOR SURGICAL PROCEDURES

Operation	Patient	Net N. Loss or Gain 10-day P.O. period
Thoracic sympathectomy	L. M.	- 27.10 Gm.
	McM.	- 68.47 Gm.
Esophagoplasty	Ril.	- 75.17 Gm.
Exploratory celiotomy	Windb.	- 65.37 Gm.
	Bernst.	- 16.86 Gm.
	Valent.	- 3.81 Gm.
Acute append. (peritonitis)	Ad.	- 49.17 Gm.
Gastric resection	Neh.	- 73.53 Gm.
	Maz.	-175.79 Gm.
Repair perforated peptic ulcer	Ly.	-136.06 Gm.
Cholecystectomy	Fish	- 24.34 Gm.
	Thomp.	- 27.78 Gm.
	Miller	- 23.18 Gm.
	Lew	- 20.74 Gm.
	Barger	- 75.90 Gm.
	Patton	- 24.73 Gm.
	Bohl.	- 68.65 Gm.
	Glynn	+ 5.91 Gm.
	Clayt.	- 36.44 Gm.
	Mal.	+ 1.13 Gm.
	Pears.	-114.09 Gm.
Radical mastectomy	Rawl.	+ 1.23 Gm.
	Meed.	- 15.68 Gm.
	Shaw	- 13.51 Gm.
Operation on extremities	Burdi.	- 9.98 Gm.
	Kit.	- 6.21 Gm.
	Gal.	- 30.00 Gm.
Thyroidectomy	Anth.	+ 4.44 Gm.
Herniotomy	Berb.	- 18.35 Gm.
Gastro-enterost.	Hag.	- 47.96 Gm.
Partial colectomies	Robert.	- 20.72 Gm.
	Boyer	- 60.22 Gm.
	Zaraz	- 51.86 Gm.
	Benk	- 49.48 Gm.
	Schr.	- 69.87 Gm.
	Ehl.	+ 4.97 Gm.
	Steph.	- 41.44 Gm.
	Thomp.	- 59.88 Gm.
Operations on pancreas	Rapacz	- 39.96 Gm.
	Fait	- 24.41 Gm.
	Cullen	- 61.02 Gm.

NITROGEN LOSS

TABLE I A

SUMMARY OF DATA IN TABLE I ON NITROGEN LOSS IN TEN-DAY POSTOPERATIVE PERIOD

(A) Group I:	18 patients lost up to 40 Gm. of nitrogen, average	= 21.31 Gm.
Group II:	7 patients lost 41 to 60 Gm. of nitrogen, average	= 51.4 Gm.
Group III:	11 patients lost 61 to 175.8 Gm. nitrogen, average	= 89.45 Gm.
Group IV:	5 patients gained 1.13 to 5.91 Gm. nitrogen, average	= 3.54 Gm.
(B) Calculated *dry weight of protein lost (Group I)	= 133.19 Gm.; this represents †0.67 Kg. wet body tissue.	
Calculated *dry weight of protein lost (Group II)	= 321.25 Gm.; this represents †1.6 Kg. wet body tissue.	
Calculated *dry weight of protein lost (Group III)	= 549 Gm.; this represents †2.7 Kg. wet body tissue.	
* Grams of excreted nitrogen x6.25.		
† Calculated on assumption that the relationship of tissue protein to water in the tissues is 1:5 (Best and Taylor: Physiological Basis of Medical Practice, 2nd ed, Baltimore, Williams-Wilkins, pp. 915-916, 1940.)		

There seemed to be no correlation between age, sex, type of anesthesia, the presence or absence of malignant neoplasm or other type of disease, and the extent of nitrogen loss. The most important factor in this connection appeared to be the period of postoperative starvation and period of limited intake of food. Moderate brief rises in temperature did not affect nitrogen excretion to a very marked degree. Indeed, the patient in whom the postoperative nitrogen loss was greatest (175.79 Gm.) had had a Pólya-type partial gastrectomy and for the ten-day period was afebrile but ate practically no food because of intractable vomiting; recovery eventually ensued. Where the individual could tolerate food relatively early and ingested a relatively liberal diet there was a small net loss or even a positive nitrogen balance at the end of the ten-day period. A study of the day-to-day nitrogen balance revealed that the major portion of the net loss occurred during the first five days postoperatively when food by mouth was not permitted or was very limited.

The practical importance of an effective method for parenteral administration of nitrogenous foodstuff in postoperative management where intake by mouth would of necessity be limited, especially for prolonged periods and in debilitated persons, is obvious. This would reduce or even prevent significant loss of nitrogen. Such a possibility would appear to be afforded by the intravenous injections of casein digest which Elman in 1937, and reporting before this Association in 1940, demonstrated for the first time to be feasible in man. Our own studies were concerned with obtaining pertinent data on the question of the clinical use of casein digests.

The casein digest (Amigen) employed by us in the observations recorded below was kindly furnished by Mead-Johnson and Company, Evansville, Ind., and represents an enzymic hydrolysate of casein (complete protein). Mueller, Kemmerer, Cox, and Barnes found that young rats on a diet, the nitrogenous portions of which consisted of the digest, grew and developed normally, and that dogs with hypoproteinemia regenerated plasma proteins with the digest given by mouth as the sole source of nitrogen. Clark, Brunschwig, and Corbin showed, for the first time, that dogs depleted of protein stores and exhibiting hypoproteinemia as a result of several weeks on a synthetic *nitrogen-free* diet regenerated plasma proteins when this diet was continued and supplemented by daily intravenous injections of the digest as the sole source of nitrogen. These experiments are summarized in Table II.

TABLE II

(Reproduced from Proc. Soc. Exp. Biol. and Med., 49 282-285, 1942)

SUMMARY OF EXPERIMENTS ON PLASMA PROTEIN REGENERATION WITH INTRAVENOUS INJECTION OF CASEIN DIGEST (AMIGEN)

Dog	Depletion period N.-free diet, days	Duration of inj., days	Avg. daily casein digest intrav. (10% sol.), c c.	Beginning		End
				of inj. period		
Eddie Exp. I	47	12	165	Wt., Kg.	6.7	6.1
				Total P.P., Gm. %	4.06	5.64
				Hematocrit	39	34.2
				R.B.C., M.	6.2	5.8
Eddie Exp. II	21	17	177	Wt., Kg.	7.0	6.2
				Total P.P., Gm. %	4.66	4.91
				Hematocrit	41	32
				R.B.C., M.	8	5.8
Fuzzy Exp. I	27	21	248	Wt., Kg.	9.2	8.3
				Total P.P., Gm. %	4.74	5.12
				Hematocrit	43	35
				R.B.C., M.	7	5.0
Fuzzy Exp. II	37	15	210	Wt., Kg.	9.1	9.2
				Total P.P., Gm. %	4.31	4.97
				Hematocrit	43	35
				R.B.C., M.	6.1	6.0
Pete	77	18	309	Wt., Kg.	7.4	6.6
				Total P.P., Gm. %	5.0	5.97
				Hematocrit	37	25
				R.B.C., M.	7.5	4.7
Mike	21	11	256	Wt., Kg.	8.6	8.1
				Total P.P., Gm. %	3.98	4.99
				Hematocrit	38.2	27
				R.B.C., M.	7.5	6.14
Kate	76	7	214	Wt., Kg.	8.1	7.6
				Total P.P., Gm. %	5.31	5.7
				Hematocrit	40	36
				R.B.C., M.	5.5	6.1

* Plasma protein.

† Red blood count.

The manner of injection of casein digest varied with the individual patient, the total amount of fluid to be administered, and the sensitivity of the patient to the injections. The product was received, sterile, in bottles containing approximately 1,000 cc. of a 10 per cent aqueous solution of the digest, thus representing 100 Gm. of hydrolyzed casein or approximately 12 Gm. of nitrogen. In these studies it was administered in one of the following forms:

- (1) Intravenously as a 10 per cent solution (hypertonic).
- (2) Intravenously with equal parts of 5 per cent or 10 per cent dextrose in distilled water (hypertonic).
- (3) Intravenously with two parts of distilled water (isotonic).
- (4) By hypoclysis, one part casein digest, two parts of distilled water (isotonic).
- (5) Intravenously as 10 per cent solution with equal parts of normal saline or Ringer's solution.

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Further data concerning the casein digest is as follows:

One hundred Gm. of digest yields approximately 12 Gm. nitrogen. One gram of digest is approximately equivalent to 3.66 calories. Studies on guinea-pigs, carried out by H. C. Hopps and J. Campbell, of the Department of Pathology, confirmed the fact that the product was not anaphylactogenic.

Additional quantities of saline or Ringer's solution may be administered to afford adequate electrolyte. Where 50 Gm. of protein were desired as supplementary nourishment, 500 cc. of the 10 per cent solution were mixed with a liter of triple distilled water and injected either by hypodermic or intravenously.

Nitrogen equilibrium can ordinarily not be achieved on a pure protein diet, thus simple injection of a quantity of digest equivalent to the standard protein requirement of a given individual will obviously not suffice to prevent nitrogen loss. Caloric requirements must be met to a substantial degree by carbohydrate (and fat) which afford energy and thus spare, so to speak, the amino-acids for protein synthesis, otherwise the amino-acids themselves will be catabolized for sources of energy. Thus, where nourishment is given entirely by the intravenous route the casein digest must be combined with glucose.

TABLE III

NITROGEN BALANCE STUDIES SHOWING FAILURE TO ACHIEVE NITROGEN EQUILIBRIUM IN PATIENTS RECEIVING QUANTITIES OF PROTEIN (CASEIN DIGEST) AND INADEQUATE GLUCOSE DURING PERIODS OF OBSERVATION

Days	Patient, J. O.*				Patient, Schoendt†				Patient, Whit.‡			
	Gm.N. Excr.	Gm.N. Inj.	Gm. Bal.	Gm. Inj.	Gm.N. Excr.	Gm.N. Inj.	Gm. Bal.	Gm. Inj.	Gm.N. Excr.	Gm.N. Inj.	Gm.N. Bal.	Gm. Dext. Inj.
1.....	8.91	0.00	- 8.91	12	5.80	+ 6.20	70	4.09	4.09
2.....	6.0	9.19	- 3.19	75	19.15	12.00	- 7.15	150	10.09	6.00	-3.91	75
3.....	26.7	12.00	- 6.70	150	22.00	12.00	-10.00	150	12.18	6.00	-6.18	75
4.....	25.30	12.00	-13.30	150	21.33	12.40	- 9.33	150	14.74	6.00	-8.74	75
5.....	26.70	12.00	-14.70	150	14.41	12.00	- 2.41	75	14.37	6.00	-8.37	75
6.....	22.60	12.00	-10.00	150	18.60	12.00	- 6.60	150	10.39	6.00	-3.60	75
7.....	20.00	0	-20.00	150	17.51	12.00	- 5.51	150	12.15	6.00	-6.15	75
8.....	20.95	18.00	- 2.95	75	17.65	12.00	- 5.65	150	12.55	6.00	-6.55	75
9.....	23.30	18.00	- 5.30	75	20.75	12.00	- 8.75	150	9.00	6.00	-3.00	75
10.....	20.10	18.00	- 2.10	75	18.59	12.00	- 6.59	150	15.02	12.00	-3.02	75
11.....	21.60	18.00	- 3.60	75	11.80	12.00	+ .20	150	13.33	12.00	-1.33	75
12.....	20.03	18.00	- 2.03	75	16.50	12.00	- 4.50	150	16.95	12.00	-4.95	75
13.....	23.30	18.00	- 5.30	75	7.75	12.00	+ 4.23	150	14.12	12.00	-2.12	75
14.....	24.60	18.00	- 6.60	75	16.00	12.00	- 4.00	150	15.14	12.00	-3.14	75
15.....	22.9	18.00	- 4.90	75	14.04	12.00	- 2.04	150	13.91	12.00	-1.91	75
16.....	27.30	18.00	- 9.30	75	19.77	12.00	- 7.77	150	16.17	12.00	-4.17	75
17.....	17.31	12.00	- 5.31	75	18.53	12.00	- 6.53	150	12.74	12.00	- .74	75
18.....	13.94	12.00	- 1.94	75	17.63	12.00	- 5.63	150	10.98	12.00	+1.02	75
19.....	15.92	12.00	- 3.92	50	22.3	18.00	- 4.30	100	7.61	12.00	+4.39	75
20.....	17.18	9.00	- 8.18	75	18.49	18.00	- .49	100	12.30	12.00	- .30	150
21.....	14.39	18.00	+ 3.61	75	22.50	8.00	-14.50	100	13.11	12.00	-1.11	75
22.....	21.30	18.00	- 2.70	75	11.64	8.00	- 3.64	100	13.23	12.00	-1.23	150
23.....	13.45	9.00	- 4.45	150	22.80	8.00	-14.80	100	9.72	12.00	+2.28	150
24.....	Total N. loss = 119.56 Gm.				17.92	12.00	5.92	63
25.....	16.75	18.00	+ 1.25	75	14.12	12.00	-2.12	63
26.....	14.74	18.00	+ 3.26	75	Total N. loss = 70.88 Gm.			
27.....	20.70	18.00	- 2.70	75
Total N. loss = 140.05 Gm.												

* J. O., M., age 23 (274746), regional ileitis, partial enterectomy, wt. 66 Kg.

† Schoendt, M., age 36 (87546), regional ileitis, partial enterectomy, wt. 81 Kg.

‡ Whit., M., age 57 (273337), Ca. stomach, total gastrectomy, wt. 61.5 Kg.

The details of the nitrogen balance in three patients receiving nothing by mouth and glucose and amino-acids in the form of casein digests over rather prolonged periods are summarized in Table III and the failure to obtain nitrogen equilibrium is well demonstrated since, while the caloric requirements were nearly satisfied, there was obviously insufficient quantity of carbohydrate to spare amino-acids. On the other hand, in patients J.O. and Whit. some of the daily losses of nitrogen were small enough to warrant the assumption that nitrogen loss was to some extent spared by the quantity of glucose injected.

It would appear that there are individual variations in metabolism and that in the exceptional instance postoperative nitrogen loss may be consistently and appreciably reduced and nitrogen equilibrium achieved with parenteral carbohydrate and casein digest, even where the proportions of

TABLE IV

NITROGEN BALANCE STUDY OF PATIENT RECEIVING NOTHING BY MOUTH AND CASEIN DIGEST AND GLUCOSE INTRAVENOUSLY, SHOWING SPARING EFFECT OF DIGEST ON NITROGEN LOSS

Mrs. Rasg. (274120), F., age 36, Ca. stomach, resection, wt. 50 Kg.

Days	Gm.N. Inject.	Gm.N. Excret.	Gm.N. Bal.	Gm. Dext. Inject.
1	0	2.46	2.46	50
2	0	2.71	- 2.71	125
3	0	9.28	- 9.28	25
4	0	19.43	-19.43	100
5	6.00	- 9.10	- 3.10	75
6	12.00	-17.13	- 5.13	75
7	12.00	-14.64	- 2.64	100
8	12.00	-12.75	.75	75
9	6.00	-13.27	- 7.27	75
10	12.00	-11.99	+ .01	50
11	12.00	-12.79	- .79	75
12	15.60	-12.81	+ 2.79	75
13	18.00	-18.84	- .84	75
14	18.00	-18.66	- .66	75
15	18.00	-18.27	- .27	75
16	18.00	-22.72	- 4.72	75
17	18.00	19.37	- 1.37	75

Total loss N. during 12-day period of injection of casein digest = 24.80 Gm.

these two foodstuffs are not ideal. The nitrogen balance studies in such a case are summarized in Table IV. During the 13 days in which the casein digest together with glucose was administered, nitrogen equilibrium was almost achieved in five days, was achieved on one day and on one day a positive nitrogen balance obtained. The total loss of nitrogen during the 12-day period in which casein digest and carbohydrate were injected was 24.80 Gm., which is no greater than in a number of patients subjected to the routine postoperative management in regard to permission for ingestion of food as soon as possible.

Where there has been depletion of nitrogen stores because of prolonged vomiting and consequent reduced intake, casein digests and carbohydrate in proper amounts and relative proportions might facilitate replenishment of the stores where this would take a longer period by ingestion of food alone, especially where the appetite is poor.

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TABLE V

SHOWING POSITIVE N. BALANCE IN PATIENT (WITH TERMINAL STAGE OF CARCINOMA) AFFORDED BY INTRAVENOUS INJECTION OF CASEIN DIGEST SUPPLEMENTING LOW PROTEIN DIET

Pt. Lak., M., age 50 (270426), wt. 60.3 Kg., inop., Ca. pancreas, prev. cholecystogastrostomy

Observation Days	Intrav. N. Gm.	N. by Mouth Gm.	N. Excr. Gm.	N. Bal. Gm.	Dext. (per os) Gm.	Fat (per os) Gm.
1		6.60	7.29	- 6.9	252	87
2		6.30	8.65	- 2.35	316	94
3		2.70	3.80	- 1.10	178	74
4	18	0	10.62	+ 7.38	0	0
5	18.00	.75	7.86	+ 10.89	100	18
6	18.00	.75	14.37	+ 4.38	112	26
7	14.00	.90	7.86	+ 7.04	100	32
8	12.00	1.95	13.52	+ .43	135	42
9	12.00	1.65	5.32	+ 8.33	116	50
10	12.00	1.50	7.56	+ 5.94	140	43
11	12.00	3.00	12.86	+ 2.14	160	78
12	12.00	1.20	13.65	- .45	105	35
13	12.00	1.75	9.74	+ 3.01	142	46
14	12.00	2.10	10.76	+ 3.24	162	53
15	12.00	1.95	4.85	+ 9.10	130	53
16	12.00	1.95	12.77	+ 1.18	139	53
17	12.00	1.20	14.68	- 1.48	122	34
18	12.00	1.20	15.48	- 2.28	157	30
19	6.00	1.00	5.35	+ 1.65	112	16

Net positive N. balance in 16-day period = 127.94 Gm. (Calculated equivalent to 4 Kg. of protein with water in the body.)

An example of this is afforded by the nitrogen balance studies of the patient summarized in Table V. He presented advanced carcinoma of the head of the pancreas, had had a cholecystogastrostomy some weeks previously and was brought back to the hospital because of increasing weakness and a recent severe gastro-intestinal hemorrhage. As shown in the table, the nitrogen balance was negative during a three-day period when choice of food was left to the patient. Beginning with the fourth day, a low protein diet was prescribed and casein digest injected intravenously each day. The plasma proteins were low (5.5 Gm. per cent) indicating a depletion of protein stores. On the combination of intravenous digest and diet by mouth, the patient was put into positive N. balance and at the end of the sixteenth day of the injection period, presented a net gain in nitrogen of 127.94 Gm. which is equivalent to 800 Gm. of protein dry weight and 4,000 Gm. of protein with water as body weight (or 8.8 lb.). Clinically, the patient did not make progress, continued to complain of loss of appetite and on the day following the last recorded studies died suddenly of massive hemorrhage into the bowel. Necropsy revealed abdominal carcinomatosis, and the source of the hemorrhage was neoplasm fungating into the duodenum from the head of the pancreas. However, these studies illustrate the possibility of forced nitrogen nutrition by the intravenous route and the avidity for nitrogen of an organism depleted of nitrogen, although there obtained a fatal disease process which was in the terminal stages.

In another series of observations, patients not suffering from a fatal condition and who were subjected to a major surgical procedure received casein digests postoperatively beginning with the day of operation and later in

supplement to the usual postoperative dietary regimen. The purpose of these studies was to obtain data on the extent of sparing excess protein catabolism. The nitrogen balance studies are summarized in Table VI, and show that in

TABLE VI

SUMMARY OF POSTOPERATIVE NITROGEN BALANCE STUDIES IN THREE PATIENTS SUBJECTED TO MAJOR SURGICAL PROCEDURES AND RECEIVING CASEIN DIGESTS AND GLUCOSE INTRAVENOUSLY FROM THE DAY OF OPERATION AND IN SUPPLEMENT TO USUAL POSTOPERATIVE DIETARY MANAGEMENT

Patient I, Mrs. T., cholecystectomy, wt. 62.9 Kg.

Days	1	2	3	4	5	6	7	8	9	10
N. Intrav. Gm.	6.00	18.00	18.00	18.00	0	9.6	0	0	0	0
N. Mouth Gm.	0	0	0	0	1.40	4.64	5.10	2.1	3.0	4.60
N. Excret. Gm.	-4.54	16.29	21.5	17.85	8.12	9.94	4.52	3.04	7.55	4.24
N. Bal. Gm.	+1.46	+1.71	-3.50	+ .15	-6.72	+3.30	+ .58	-.94	-4.55	+.36
Dext. Gm.	75	75	90	105	80	81	79	65	115	107
Fat (per os) Gm.					10	47	48	21	40	43

Net N. loss 10-day period = -8.5 Gm.

Patient II, Mr. L., cholecystectomy, wt. 80.5 Kg.

N. Intrav. Gm.	18	18	18	18	18	18	18	18	18	0
N. Mouth Gm.						0.45	6.70	6.70	9.6	12.6
N. Excret. Gm.	13.71	23.3	28.4	23.17	20.79	17.69	17.69	14.3	10.05	8.1
N. Bal. Gm.	+4.29	-4.70	-10.4	-5.17	-2.79	+.76	+7.10	+10.40	+17.10	+4.50
Dext. Gm.					160	24	160	213	260	337
Fat (per os) Gm.						98	107	82	140	152

Net N. gain 10-day period = 20.39 Gm.

Patient III, Mrs. S., cholecystectomy, wt. 76.6 Kg.

N. Intrav. Gm.	6.00	6.00	12.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00
N. Mouth Gm.	0	0	0	0	0	4.00	6.40	8.00	11.10	13.25
N. Excret. Gm.	3.32	7.54	16.57	13.26	12.00	7.16	8.59	11.36	10.98	12.00
N. Bal. Gm.	+2.68	-1.54	-4.57	-7.26	-6.00	+2.84	+3.81	+3.64	+4.12	+7.25
Dext. Gm.	150	150	300	161	175	120	161	205	190	249
Fat (per os) Gm.				4	0	33	78	75	101	108

Net N. gain 10-day period = 4.97 Gm.

one case the net loss of nitrogen was only 8.5 Gm., in one there was a net gain of 20.39 Gm. and in the third a net gain of 4.97 Gm. These were not selected cases and indeed did not present entirely smooth immediate postoperative courses. Patient I also suffered from severe menopausal symptoms and complained of severe nausea with frequent vomiting during the first four days (not due to ileus or postoperative dilatation of the stomach). Patient II was a chronic alcoholic and developed temperatures of 102° F. on the second and third days. Patient III was very apprehensive following the operation and resented all parenteral fluids. The casein digest was given to this patient by hypodermoclysis on all but the third day.

The vast majority of patients subjected to major surgical procedures recover without special attention to nitrogen balance, since the brief period of total and relative nitrogen starvation is well tolerated by the organism and the loss is made good after return to full diet. However, following major surgical operations there is frequently a rather prolonged asthenia which is often appreciable for a few weeks after discharge from the hospital. Leriche has referred to this syndrome, which cannot be clearly defined as "maladie postoperative," and ascribed it to generalized disturbances of the sympathetic nervous system. It is interesting to speculate on the possible rôle of postoperative nitrogen loss in this connection. While the quantity of tissue pro-

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tein lost may not be large, the source of the catabolized protein under these conditions is not known and might conceivably differ from the stores depleted, when in the course of usual activities the subject may simply refrain from protein foods and continue his activities. Patient II in Table VI in whom there was a net gain of 20.39 Gm. commented upon the fact that he felt quite well at this time and did not experience the weakness which he had expected to occur for some days following the operation. His weight a day before operation was 80.5 Kg. and on discharge on the sixteenth day was 80 Kg., a net loss of 0.5 Kg. or 1.1 pounds. It would be difficult indeed to evaluate the benefits in any large series of patients derived from substantial sparing or actual prevention of postoperative nitrogen loss, but it is understandable theoretically that in such a group the period of impaired physical activity due to postoperative asthenia might be shortened.

Minimal caloric requirements including sufficient protein (as amino-acids) may be met by intravenous nutrition and in this way facilitate operative procedures and contribute to recovery. The nitrogen balance studies shown in Table VII are of a white female patient, age 36, in whom a large fungating

TABLE VII

SUMMARY OF NITROGEN BALANCE STUDIES IN PATIENT WITH OBSTRUCTION IN SIGMOID DUE TO INFLAMMATORY MASS IN PELVIS

Mrs. R. F., age 36 (276536), wt. 50 Kg. Left tubo-ovarian abscess with adhesions to sigmoid colon producing obstruction

Days	N. Inj. Gm.	N. by Mouth Gm.	N. Exc. Gm.	N. Bal. Gm.	Carbohydrate Gm.	Fat Gm.
1	18.00	0	4.98	+13.02	300	
2	18.00	0	10.32	+7.68	300	
3	18.00	0	10.60	+7.40	300	
4	18.00	0	12.30	+5.61	300	
5	18.00	0	15.16	+2.84	300	
6	18.00	0	14.10	+3.90	300	
7	18.00	0	17.45	+ .55	300	
8	18.00	0	15.58	+2.42	300	
9	18.00	0	13.80	+4.20	300	
10	18.00	0	14.78	+3.22	300	
11	6.00	0	8.59	-2.59	300	
12	6.00	0	7.03	-1.03	150	
13	6.00	0	5.00	+ .91	0	
14	12.00	0	12.68	- .68	150	
15	12.00	0	16.92	-4.92	150	
16	18.00	0	13.00	+5.00	300	
17	8.4	0	14.12	-5.72	150	
18	0	1.00	8.04	-7.0	53	15
19	0	1.98	4.41	-2.43	99	30
20	6.00	7.00	9.15	-1.17	126	18
21	6.00	7.2	7.57	+5.43	184	98
22	6.00	6.04	7.29	+4.75	211	93
23	6.00	6.10	5.44	+6.66	158	83
24	6.00		8.96			

mass was excised from the cervix on the gynecologic service. Because of the histologic diagnosis of leiomyosarcoma external radiation was given. A left adnexal mass was also palpated and regarded as an extension of the tumor with inflammation. Frequent nausea and vomiting occurred at home for a number of days after discharge from the hospital. She was readmitted and

the symptoms continued for some ten days, the patient retaining almost nothing by mouth but receiving fluids parenterally. When one of us (A. B.) was requested to see the patient because of the question of low colon obstruction, there was moderate distention of the abdomen and rectal examination revealed what appeared to be constricting boggy about the rectal colon. Barium enema revealed a high degree of obstruction over several centimeters of a redundant segment of the lower sigmoid in the pelvis. The stomach was aspirated and a small quantity of liquid recovered. Nothing was then permitted by mouth. Intravenous nutrition was carried out daily by means of the following solutions:

- (A) 1,500 cc. 10 per cent casein digest } mixed in the flask
 1,500 cc. 10 per cent dextrose }
 (B) 1,500 cc. 10 per cent dextrose in normal saline

After solution A was injected, solution B was poured into the flask. The total period of injection lasted five to six hours, the total daily fluid intake was 4,500 cc. The patient soon learned at what rate nausea and other disagreeable sensations could be avoided and the clamp on the tube from the flask was placed within her reach so that she regulated the speed of intake herself.

The caloric content of the above solution is:

$$\begin{array}{rcl} 150 \text{ Gm. casein digest} \times 3.66 & = & 549 \text{ calories} \\ 300 \text{ Gm. dextrose} \times 4.00 & = & 1,200 \text{ calories} \\ \hline & & 1,749 \text{ calories} \\ \text{NaCl content} & = & 13.5 \text{ Gm.} \end{array}$$

Since the patient weighed approximately 50 Kg., the caloric content equaled 35 calories per Kg., and the protein content equaled 3 Gm. per Kg. The salt content is slightly in excess of the quantity (10 to 12 Gm.) usually ingested by adults on a general diet. Thus basal dietary requirements in energy and protein seem to have been satisfied, although of course vitamins and complete variety of minerals were not provided since it was not anticipated that complete parenteral nutrition was to be maintained for an unusually prolonged period. This factor, however, may easily be adjusted. The nitrogen balance studies show a positive balance over the ten-day period when 18 Gm. of nitrogen were injected (1,500 cc. 10 per cent casein digest) each day; on the eleventh and twelfth days of observation the latter injections were reduced to 500 cc. per day. Clinically, the patient improved markedly on parenteral nutrition. Nausea and vomiting soon ceased, distention disappeared, and gas was passed per rectum. A second barium enema taken on the eleventh day of the injection period showed disappearance of the obstruction in the lower sigmoid except for one point of partial constriction. An exploratory celiotomy was performed on the thirteenth day of the study and the left lower quadrant mass found to be a tubo-ovarian inflammatory process. This was removed dissecting about 15 cm. of adherent sigmoid colon from it. As seen in Table VII, a slight positive nitrogen balance was maintained on the day of operation and a slight negative balance obtained on the following day. Due

to the long period of intravenous injections, even prior to the use of casein digests, the superficial veins were rendered unfit for further intravenous therapy by the fifth day after operation. Furthermore, in view of the removal of the obstruction in the lower sigmoid, a soft diet was permitted by mouth and 1,500 cc. of 3.5 per cent casein digest injected subcutaneously as supplementary nourishment on the eighth to twelfth postoperative days. A review of the data shows that during the course of this study a positive nitrogen balance was maintained with caloric requirements throughout the 12 days prior to operation, the patient receiving nothing by mouth. A net gain in nitrogen amounting to 47.22 Gm. was observed in this period. For the 12 days postoperative, there was a daily variation in nitrogen balance, food was permitted on the sixth day and supplemented by continued parenteral nitrogenous nutrition. At the end of the twelfth day, the net nitrogen gain was 0.63 Gm. for the postoperative period; practically, nitrogen equilibrium was maintained. For the whole 24-day period during which food was taken by mouth only for the last five days, caloric requirements were for the most part met and the net nitrogen gain was 47.85 Gm.

Untoward Reactions.—While the administration of the casein digest was not in our experience with hundreds of individual injections accompanied by serious reactions (with exceptions to be noted below), minor disturbances were frequent. These include mild and occasionally severe nausea, and vomiting and a generalized disagreeable flushing sensation. In the exceptional instances, these are sufficiently pronounced to warrant discontinuation of injections after one or several attempts. On the other hand, we have observed nausea and a generalized feeling of discomfort to be present during the first few injections and to disappear subsequently as they are continued. In one patient marked nausea developed with the first injections but after several days she was observed to eat simultaneously while receiving the digest intravenously. An important factor is the speed of injection. This should be altered with each patient. Some individuals exhibited no discomfort from 500 cc. of the 10 per cent aqueous solution administered in 30 to 45 minutes. Where intravenous injections are not well tolerated, a 3.3 per cent solution in distilled water may be given safely by hypodermoclysis without discomfort and without reaction in the tissues. Another feature frequently encountered, is reduction in desire for food apart from any nausea or other discomfort. Patients with clinical icterus are not suitable subjects for intravenous injections of the casein digest, since in three instances severe chill, marked rise in temperature, and profound discomfort resulted from the initial injection. In another instance, a chronic alcoholic with marked liver damage, as shown by the hippuric acid liver function test, a similar reaction accompanied the initial intravenous injection but hypodermoclyses of the 3.3 per cent solution were well tolerated for several days. On the other hand, patients who had been icteric and the latter condition cleared, did tolerate intravenous administration of the digest. It would appear that in certain types of acute hepatitis a sudden flooding of the circulation with amino-acids is too great a physiologic load for

the liver to tolerate. Postmortem studies of nine patients who received substantial quantities of casein digest during their terminal disease failed to reveal evidence of toxic effects ascribable to the digests.

SUMMARY

(1) Nitrogen balance studies in 41 patients subjected to a variety of major surgical procedures revealed a net loss of nitrogen for the first ten-day period which varied widely from 3.81 Gm. to 175.79 Gm. in 36 patients. The loss was sustained for the most part during the first five days. In five instances, there was a slight net gain of nitrogen during the postoperative period due to early return to full diet.

(2) The most important factor in the nitrogen loss is the restricted ingestion of food combined with the general physiologic disturbances accompanying a major surgical procedure.

(3) Using the nitrogen balance as criterion, casein digest administered intravenously in proper proportion with glucose is effective in reducing or even preventing postoperative net loss of nitrogen and thus spares the organism from the effects of excessive protein catabolism.

(4) Casein digest and glucose intravenously may be employed as the sole source of nutrition, affording at least minimal caloric requirements under certain conditions, and include an adequate supply of amino-acids to maintain nitrogen equilibrium, or even afford a positive nitrogen balance in patients with depleted protein stores.

(5) Whether or not a surgical procedure is performed or contemplated, intravenous administration of casein digest is a means of forced nitrogenous nutrition.

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DISCUSSION.—DR. WARREN M. COX (Evansville, Indiana): I sincerely appreciate this opportunity to comment upon the papers by Doctor Brunschwig and Doctor Elman. As a biochemist, I cannot make any comment on their clinical observations. Our attention has been centered on the hydrolysate, its preparation, and more particularly its biologic utilization. Last week some of our studies in this regard were presented at the Federation meetings in Boston, and part of those may be of interest to this group.

We were particularly interested in the synthesis of serum albumin as effected by the intravenous administration of the casein hydrolysate. Others have made observations in this regard. Thus, some years ago Doctor Elman made observations that regeneration would be effected both in animals and in a few clinical cases.

Doctor Madden, in Doctor Whipple's laboratory, made an observation that regeneration could be effected in dogs made hypoproteinemic by plasmapheresis, and Doctor Brunschwig showed his results in this regard this morning.

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We were interested, however, in knowing, quantitatively, whether the casein hydrolysate administered intravenously would have the same effect as casein or the hydrolysate given by mouth. For this purpose, we followed the procedure of Weech, in which dogs are made hypoproteinemic by low protein diet. They are fed this diet for three weeks. Following this, they are given protein at an intake level of 2.5 Gm. per kilo and caloric intake level of 80 per kilo, for a period of one week. The amount of regeneration during this one week's period constitutes the measure of efficiency of the protein.

Thus, we fed one group of dogs the casein hydrolysate by mouth, and another similar group the casein hydrolysate by vein. The material was given in 10 per cent solution in sterile form, and if we may have the first slide, we can see the results.

(Slide) The albumin values are given in the first column on the left. This column gives the decline of serum albumin during the standardized depletion period. Here we have the regeneration when the material was given intravenously, and here is the assay value as employed by Weech. You have an average assay value for the casein hydrolysate given intravenously of 0.43. By mouth—this is really a total of 21 animals—you have a regeneration average of 3.5. These figures are in entire agreement with the values previously reported for casein by mouth, so that we can say that casein and casein hydrolysate by mouth and casein hydrolysate by vein have the same effect on serum protein regeneration.

In conclusion, I think we might say that this means that casein hydrolysate by vein has about the same effect as beefsteak by mouth.

DR. OWEN H. WANGENSTEEN (Minneapolis, Minn.): Owing partly to the work of Doctor Ravdin of this Association, and to Dr. George H. Whipple, of Rochester, N. Y., the attention of all of us has been focused on the great importance of meeting or attempting to meet the protein requirements of the surgical patient. It remains, however, for Dr. Robert Elman of this group to indicate that it is feasible and practical to maintain satisfactory nitrogen equilibrium with the administration of amino-acid.

Those two Danish observers, Henrique and Anderson, I think just prior to the last war, showed that in a goat that casein hydrolysate could be utilized to advantage in establishing nitrogen equilibrium.

I think most of us, with any experience at all, know that you can inject practically without any reaction and that it would be fair to say that surgeons have been quite remiss in their attitude toward the feeding of surgical patients. I think, in a sense physiologists have contributed to this dereliction or delinquency of ours, in that they have not only pointed out but have emphasized that periods of starvation may not only be well-borne but some have affected to believe that in such periods of starvation, mental and even physical efficiency are improved.

Anyone who has given the matter serious concern with reference to surgical patients will understand there is a difference. We are dealing with ill patients. We are dealing with patients who, perhaps, come to us from periods of starvation, and we as surgeons now, owing to the stimulation the problem has had from Ravdin, Whipple, Elman, and others, affect to manifest an interest in the problem. Our performance, in a sense, belies that manifested or professed interest, for we do not begin to meet caloric requirements of patients or nitrogen requirements. I think most of us have been content to meet water and electrolytic requirements only. I contend that in the immediate future surgeons must have an eye to meeting not only water and electrolytic requirements but also those of calories, nitrogen, mineral, and vitamin requirements.

The magnitude of the problem imposed upon the surgeon in trying to do this is manifest in these slides that have been shown you by the two preceding speakers.

My associates and I, as Doctor Elman said, are interested in the problem of trying to maintain nitrogen equilibrium with human plasma. More than two years ago we published a paper indicating that nitrogen balance could be maintained in such a manner. Perhaps it is necessary to point out that there is a fundamental difference in behavior when plasma is injected intravenously and when amino-acid is injected. When one uses protein plasma and the nitrogen intake of the urine is reduced to a low level through the use of glucose ingested by mouth or given intravenously, there is no augmentation of excretion of nitrogen in the urine. All the plasma given intravenously is available for storage, and you quickly raise the level of plasma protein.

On the contrary, when one injects amino-acids, only so much of the amino-acids are available for energy requirements, unless calories are given in large quantity, that you have to inject larger amounts. So the matter of dosage comes in. I suppose it would be fair to say that for a man who weighs 70 kilos an optimum requirement of protein in the order of magnitude of something like 70 Gm. is necessary to maintain nitrogen equilibrium.

There are many practical problems involved in this issue. It is obvious, of course, that we are dealing essentially with starved surgical patients. Patients with obstruction to pyloric outlet present an ideal problem about which to discuss this situation.

In our own clinic, now for more than two years, we have done no two-stage operations in such patients. We have only done one-stage operations, feeding the patient intravenously with glucose and amino-acid and plasma. I do not believe that glucose is the ideal solution. I hope sometime we will have an agent by which we can administer the required amount of calories and not thrombose the veins, as we are likely to do in using 20 per cent glucose, and not give too much fluids and overhydrate our patient, if he is very old, and lose him through the agency of pneumonia and cardiac failure.

I think the papers are very pertinent, and it is a subject in which we will all have to manifest a greater interest.

DR. HARVEY B. STONE (Baltimore, Md.): I should like to ask Doctor Elman whether he will enlighten me, in closing, on one point. Does the administration of these protein split products which may be used for regeneration, as I understand it, either of the tissue proteins or of the serum of the plasma proteins, exert the same osmotic pressure when administered as the administration of plasma does? In other words, will it serve the same purpose in the physiochemical maintenance of fluid balances between tissue spaces and circulation that can be expected from the administration of serum plasma?

DR. ALEXANDER BRUNSCHWIG (closing): There is just one more point I would like to emphasize. In our experience we have found what we think is one absolute contraindication to the injection of casein digest, and that is icterus or marked liver damage, as being discovered by appropriate liver function tests. We attempted to build up, so to speak, three icteric patients showing carcinoma of the pancreas, the icteric indices in these patients ranging from 40 to 120, and in each case a very severe chill and rise in temperature, which promptly dropped in a few hours, occurred. The patients felt very uncomfortable. Their appearance was quite alarming at the time.

In another patient, a chronic alcoholic, who had no icterus, but whose liver function, by the hippuric acid test, was very low, there was also a very severe reaction.

Apparently the liver, when it is abnormal, cannot cope with a flooding of the circulation by amino-acids, and this reaction results.

We have observed, however, that a patient who will exhibit the reaction as a result of intravenous injection does tolerate subcutaneous injections very well without reaction. In our experience a 3.3 per cent solution of casein digest in distilled water can be given repeatedly day after day, just as one would give isotonic saline or 5 per cent glucose.

We have also observed that in patients in whom the liver function test is very low and who did exhibit a reaction resulting from one of the injections of casein digest, when the hepatitis improved to some extent they could tolerate intravenous injections. One patient who had an icteric index of over 80, and in whom we did not want to risk an intravenous injection subsequently, received intravenous injections after the icteric index had been normal for about two months, without any untoward effect.

DR. ROBERT ELMAN (closing): It has, of course, been quite impossible to touch on anything but the bare essentials of all the implications of the new method of therapy.

In answer to Doctor Stone's question, these amino-acid mixtures have osmotic pressure which is similar to that of glucose. Therefore, in order to exert the same colloidal pressure as protein they would have to be synthesized in the serum protein. But the matter is not as simple as that, because we have observed on many occasions a very pronounced diuresis, a passage of fluid from edematous intestines, in intestinal obstruction, etc., following the injection of amino-acids, without very much significant increase in the serum protein concentration. We have been tempted to believe that the amino-acids

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in some way lead to an increased nutrition of the tissues, perhaps the capillaries, which enable the food to flow in the right direction, namely, into the lumen of the blood vessels and out through the kidneys, and relieve the edema of various body tissues.

It seems sort of presumptuous to bring up this point again, which has been emphasized by Doctor Wangensteen, namely, that food is important for life, and yet we see patients on surgical wards being given all sorts of vitamins because of the emphasis and the publicity they have received, and yet many of them are starving to death.



AIR-RAID SHELTER PROPHYLAXIS

A method of prophylaxis which, we are informed, may be introduced into the shelters can be properly commented upon by a surgeon—namely, the provision that has been made for the wearing of masks to prevent the spread of droplet infection. We are told that half a million masks are ready to be distributed as and when required. Surgeons have long acted upon the view that infection can easily be transferred by means of the breath, and the wearing of masks is a routine in the operating theatre. The human nasal and pharyngeal mucosa is in some cases as susceptible to infection as an open wound, and I have often been surprised that physicians have not strongly preached, and by force of example demonstrated, that contagion of the common influenzal cold could be prevented by the wearing of an efficient mask. If in the shelter, why not in the work-room or office? Making the reasonable assumption that in Great Britain every year one million people lose one day from work as the result of a cold, the time lost from this cause annually would equal nearly 3,000 work-years. Would it not be worth attempting to reduce this time by mask prophylaxis?

—V. Zachary Cope, M.D., British Medical Journal.

SYMPOSIUM ON BURNS

CLINICAL AND EXPERIMENTAL STUDIES WITH THE KOCH METHOD OF TREATMENT OF HEAT BURNS*

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THE PURPOSE of these studies has been an effort to determine the effect of primary pressure dressings upon the loss of plasma from the burned area and into the surrounding tissues.

CLINICAL STUDIES

In our approach to the clinical problem we have, like Koch and many others,^{1, 2, 3, 4} regarded burns as badly contaminated serious wounds and, in the preparation of the patient for the dressing, have employed the fundamental surgical principles which many of us have advocated for the treatment of wounds in general. However, for a proper evaluation of these studies it seems to us best to describe in some detail the exact procedures we have followed.

Preoperative Period.—This is devoted to an assay and treatment of the patient's general condition and an effort to lessen further contamination of the wound. At the site of the accident or in the first-aid stations we try to prevent the use of ointments, oils and various "home remedies" by advocating the use of a dry, clean sheet, piece of cloth, or a towel when dry sterile dressings are not available. The patient should be kept warm with blankets under and over him. Hot drinks in small amounts may be given. Morphine in adequate amounts to produce sedation is given as soon as available. The patient is taken to a hospital as soon as possible.

In the hospital all persons connected with the care of these patients should be properly capped and masked. A rapid survey and physical examination is made without disturbance of either the patient or the dressings. In extreme cases we have administered oxygen during this period.

As soon as possible a 2 cc. heparinized blood specimen is sent to the laboratory for hematocrit† and plasma protein determinations. These initial values are considered the base line. If the burn, however, is a serious one,

* Read before The American Surgical Association, Cleveland, Ohio, April 6-8, 1942.

† The method employed for the hematocrit determination is that advocated by Guest and Siler.⁵ As mentioned, 1-2 cc. of heparinized blood is sufficient for both hematocrit and plasma protein determinations. From this vial of blood, thin-walled capillary tubes in pairs are partially filled. One end is sealed in a microflame and the tubes thus filled and sealed are centrifuged in a special carriage until the cells are packed to a constant

KOCH METHOD OF BURN TREATMENT

that is, 25 per cent of body surface or more, we do not wait for the laboratory report, but immediately expose a vein in some unaffected site, usually the ankle, and start plasma transfusion. Our experience is that one-half normal plasma given by intravenous drip is best in the early stage of the injury. Only in very rare instances have we seen a burn of such magnitude that a

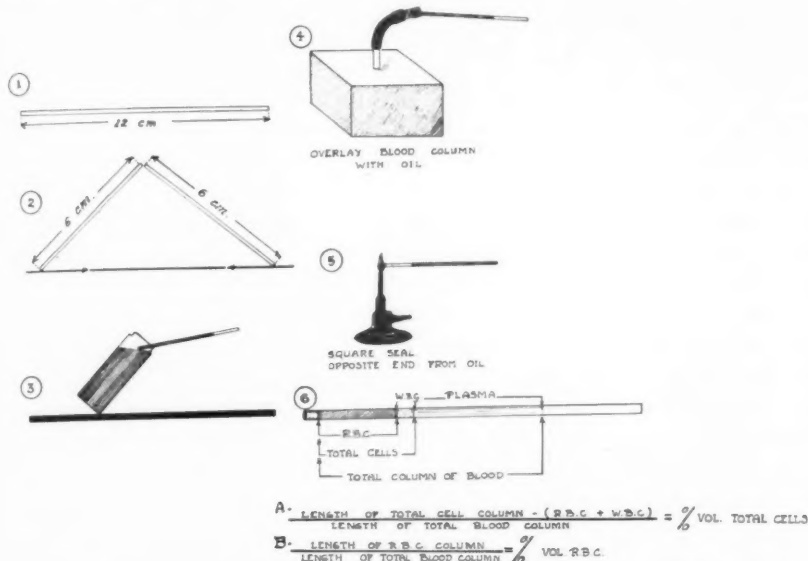


FIG. 1.—Diagrammatic sketch showing the technic for capillary hematocrit determination. (1) A 12 cm. capillary tube. (2) Same tube divided into two 6 cm. capillary tubes. (3) Capillary tubes filled two-thirds full with heparinized blood. (4) Method of placing paraffin oil over blood column to prevent evaporation of plasma. (5) Technic for sealing open end of capillary tube. (6) Capillary tube after centrifugation. Measurements made by microscope equipped with graduated mechanical stage. (A) Calculation for per cent volume of total cells. (B) Calculation for per cent volume of R.B.C.

site for venous cannulization could not be found. When this does occur one is certainly justified in giving intrasternal plasma transfusion, a route sometimes forgotten. When we feel that the condition of the patient will permit it the second phase of treatment is begun.

volume. The columns of cells and plasma are then measured by means of a microscope which is equipped with a cross-hair eyepiece and a graduated mechanical stage. From these measurements the volume of "total" cells and "red blood cells" are calculated in percentage of whole blood (Fig. 1). The principal advantages of the capillary hematocrit method are that it is economical of blood; that the anticoagulant used does not affect the size of the cells; that the volumes of red cells and white cells may be read separately with ease; that errors due to rubber sealing devices are avoided; and finally that it is rapid. The entire procedure including calculations requires less than ten minutes. This is a particularly important factor in the treatment of "thermal shock" and also important to the technician who may be required to do as many as 20 to 30 such determinations daily.

While the hematocrit tubes are being read the remaining 1-2 cc. of heparinized blood is spun in a special angle centrifuge head. From this plasma a protein determination is obtained using the Guthrie modification of the Barbour-Hamilton "falling-drop" apparatus. This procedure requires five to eight minutes.

Operative Treatment.—In this stage of the management of burns an effort is first made to convert a contaminated large wound into a clean wound. The patient is placed on the operating table upon a sterile sheet. In most instances general anesthesia is administered. Intravenous therapy is continued as indicated by the general condition of the patient and the laboratory tests. The surgeons and nurses, who have been gowned and gloved in the usual fashion, after scrubbing for ten minutes, drape the involved region with sterile towels and sheets. The wound is gently but thoroughly washed with white soap and water. The soap is irrigated from the area with physiologic saline solution. Gross débridement is carried out during this procedure; that is, all of the necrotic skin and blisters are removed. The surgical team changes gown and gloves, after which the area is redraped. Using fresh instruments and containers, a more minute débridement is now done and the wounds are gently washed with white soap and water the second time. Irrigation is again carried out with physiological saline solution.

The pressure dressing is then applied as follows: The wound is first covered with sterile fine mesh single thickness vaselined gauze strips on top of which are placed flat gauze dressings followed with fluffed sponges. Pressure is exerted upon the area with a folded gauze roll. Further compression is obtained not only upon the wound itself, but also upon the surrounding tissue by placing sterile "mechanic's waste or cotton" over the entire region. The latter is held in position with a sterile muslin roll. The dressing is made a complete surgical one by means of adhesive tape which maintains the pressure and aids in immobilization of the involved part. If necessary, either sterile aluminum splints are incorporated in the dressings as in the case of an involved forearm or hand, or immobilization of the lower extremity is maintained by the application of light plaster encasements. This dressing is allowed to remain untouched, usually, for from ten to fourteen days. In the case of first- and second-degree burns the wound should be completely healed when the dressings are removed, while in the case of third-degree burns, the wound usually allows the application of a split-thickness graft, as advocated by Blair and Brown. If there is mild infection of the granulating wound, postage stamp Thiersch grafts may be safely applied. In the rare instances of gross infection, the wound must be further prepared for grafting by suitable means.

Postoperative Care.—Since no further care of the wounds is necessary for a long period of time, the main problems are concerned with the treatment of the patient's general condition and good nursing care. In the severe case, a continuation of all the laboratory tests and therapeutic procedures, utilized preoperatively, may be necessary for several days. We refer particularly to the use of the hematocrit, specific gravity and plasma protein determinations of the blood for the control of fluid and plasma therapy.⁶

Results.—We have, during the past two years, used this method of primary cleansing, compression, and rest treatment of burns on 134 patients. Of this number, 90 were children and 44 were adults. From the standpoint of the

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extent of the burns, as measured by Berkow's method, the cases may be divided as follows: Less than 15 per cent of body surface, 39 cases; 15 to 30 per cent, 58 cases; 30 to 60 per cent, 27 cases; 60 to 85 per cent, nine cases; 85 per cent or over, one case (Table I).

TABLE I

NUMBER OF CASES TREATED IN THIS SERIES REGARDING PER CENT OF BODY SURFACE INVOLVED AND DEPTH OF BURN

Depth of Involvement	Per Cent of Total Body Surface Involved					Total Cases	Per Cent
	Degree of Burn	15% or Less	15%-30%	30%-60%	60%-85%	85% or More	
1° and 2°.....	11	20	12	43	32
3°.....	4	6	3	13	10
1°, 2° and 3°...	24	32	12	9	1	78	58
Total Cases....	39	58	27	9	1	134	
Per Cent.....	29	43.8	20	6.7	0.7		100

In this series of 134 cases there were five deaths, or a mortality rate of 3.7 per cent. Of the five patients who died, three were given a general anesthetic and the other two were treated under analgesia. Among these three anesthetized patients the causes of the deaths were as follows: One, an adult, with a 40 per cent burn, died on the fourth postoperative day from a cerebral accident. Another was a child, with a 40 per cent burn, who died of asphyxia from laryngeal obstruction on return from the operating room. The third, who had a 60 per cent burn, died five hours after treatment. The exact cause of death is unknown, but was explained by a persistently high hemoconcentration in spite of large amounts of plasma therapy. No autopsies were performed upon any of these cases.

Two patients died who were treated under analgesia. One, an adult, with an 85 per cent burn, died on the fourteenth postoperative day from pneumonia, empyema and pericarditis. There was a left mild hydronephrosis from a mechanical ureteral blockage. Autopsy was performed on this case. The other, a child, had a 70 per cent burn, and died 12 hours after injury, in a state of hyperpyrexia. No autopsy was obtained on this case (Table II).

TABLE II

MORTALITY RATE AND ANALYSIS OF DEATHS IN THIS SERIES OF CASES

Total Cases		Deaths	Mortality Rate	
134		5	3.7%	
ANALYSIS OF DEATHS				
Deaths	Per Cent Body Surface Involved	Time Survived	Cause of Death	Remarks
1	40	4 days	Extensive burn. Cerebral accident	Anesthesia
2	40	3 hours	Extensive burn. Asphyxia	Anesthesia
3	60	5 hours	Extensive burn. Not explained	Anesthesia
4	85	14 days	Extensive burn. Pneumonia-empyema-pericarditis	Analgesia
5	70	12 hours	Extensive burn. Hyperpyrexia	Analgesia

Clinical studies of the various wounds regarding infection has been most difficult. Carefully controlled bacteriologic studies were not available in this series of cases. Clinically, 79 cases had no infection; 15 cases were mildly infected; 25 cases were grossly infected, and in 15 cases the results are unknown (Table III). There were only a few minor infections in the

TABLE III
CLINICAL SURVEY OF THE WOUNDS AND INFECTION
Degree of Burn

	1° and 2°	3°	1°, 2°, 3°	Total	Per Cent
No infection.....	34	2	43	79	58.9
Mild infection.....	4	6	5	15	11.1
Gross infection.....	2	3	20	25	18.6
Result unknown.....	3	2	10	15	11.1
Total.....	43	13	78	143	100.0

first- and second-degree burns. In the third-degree burns, where grafting could not be done at the first dressing, the inevitable bacterial contamination of the granulating surfaces led to no serious local wound infections. There were no deaths due to infection, unless the one patient with an 85 per cent burn, who died 14 days after the operation from streptococcic pneumonia, empyema and suppurative pericarditis, had her portal of entry for these complications in the burned area.

Discussion of Clinical Studies.—Although careful clinical and laboratory studies have been made upon this series of patients we are faced with the difficulty of not having a satisfactorily controlled series treated by any other method for comparison. In fact, the variation in individuals and the extent of burns as they ordinarily occur in accidents make it very difficult to run a parallel series with any degree of scientific accuracy. We have not attempted to do it. The advantages of this method of therapy must, therefore, be stated more or less in terms of clinical observation of the various doctors and nurses working in the department of surgery, many of whom have had considerable experience with other forms of therapy.

The decrease in the amount of suffering by this method of treatment seems to be very striking. Rarely is it necessary to continue to use morphine or codeine for more than a day or two after operation. The patients can move about much more easily. The nursing problem is greatly simplified. There is a great saving in the cost of dressing materials when compared with other methods which require frequent dressings or compress therapy. The temperature charts seem to us to show a surprisingly rapid return to normal levels.

Using "primary cleansing, compression, and rest treatment of burns," we have found, particularly in the case of children, as well as adults, that these patients rapidly assume their own water balance by oral fluid intake and that parenteral administration is only required in the more severe cases. These patients are given a high protein diet as soon as possible and it has been our experience that solid food is enjoyed early in their convalescent period.

It is our belief that the careful toilet of the wound, under anesthesia, and the long duration of the primary dressing markedly lessen the incidence of infection. The ease with which most of the patients can be restored to a normal physiologic state suggests to us that the pressure dressing may aid materially in preventing the loss of plasma at the site of the wound and into the surrounding tissues.

The dressings, as we have applied them, put the burned wounds at rest, aid the healing, help prevent infection and promote the comfort of the patient.

At the present time we are running a series of burned cases in which a sulfonamide drug is used systemically, and occasionally locally, in addition to the Koch method of treatment. It is too early in the study to draw any definite conclusions. In the series reported in this paper no sulfonamide drugs were employed.

EXPERIMENTAL STUDIES

In an effort to avoid some of the pitfalls of uncontrollable clinical studies, it was decided to try to determine upon laboratory animals the effect of pressure dressings upon the loss of plasma in and about the site of burned areas. For this purpose it was decided to use dogs, even though they do not blister from burns as do humans.

After considering the problem of an attempt to find if there is any actual difference between a burn which has a pressure dressing applied on it and one which has not, we felt that the observations which could be controlled and measured more accurately than any other were the volume-per cent red cells of the blood and the plasma protein content. It should be clear that these two determinations do not attempt to measure the amount of plasma loss, but may indicate the degree of shift of water balance in the blood. It would follow then that these two determinations would be more indicative in a comparative study and more applicable to the phenomenon of "thermal shock" seen in man than perhaps any others.

METHOD

This study in burns utilized the principle of experimenting upon animals in pairs. Dogs were used, and they were paired as well as possible from the standpoint of equivalent size, weight, and health. All of the burned dogs were given essentially the same diets for at least two weeks before any observations were made.

At varying periods, for a week before the burning injury, blood samples were obtained upon which hematocrit and plasma protein determinations were made. All of these blood samples were taken at practically the same time of day. This gave us a fairly good base line as to their normal values for these two determinations. Usually the hair was shaved off of the entire back, abdomen and both hind legs the night before each experiment, and on the following morning the animals were placed and tied into position on the tables. Equivalent areas were then outlined with brilliant cresyl green

on each animal, after which the skin of both was cleansed with soap and water for ten minutes. This area in most instances represented between 15 and 25 per cent of the body surface. Anesthesia was induced by intravenous sodium nembutal. A gas-oxygen flame was used to burn the animals. This flame was kept at a constant length, and the burner was kept at a relatively constant distance from the skin of each animal. Each pair of dogs was burned for the same period of time as determined with a stop watch.

On one dog a pressure dressing was applied to the burned area and to the surrounding soft tissue, similar to the pressure dressing which we have used in the clinical treatment of burns. After application it was enclosed

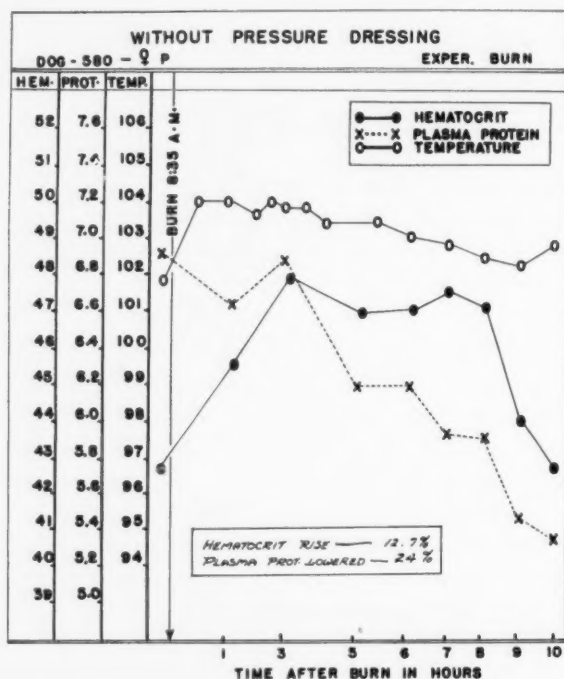


CHART 1.—Representative graph of hematocrit and plasma protein observations in an animal *without* a pressure dressing over the burned area.

in a light plaster encasement so that the animal could not disturb it. On the other hand, the second animal received no dressing at all. We believe that this procedure represents a fairly good approach to the problem of producing equivalent degrees of injury in two experimental animals.

Before the experiment was begun each animal had a sample of blood withdrawn for hematocrit and plasma protein determinations. After the animals were burned blood samples were taken every hour for three hours, and then every two hours, until a total of eight such specimens were obtained. We found that this method of blood sampling was sufficient to cover the maximum degree of hemoconcentration thus obtained. Also, the tem-

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perature, pulse, and respirations were observed before burning and at the time each sample of blood was drawn.

A group of 12 animals, or six pairs, were observed in this study. In these experimental animals a degree of hemoconcentration was seen in all cases and, as would be expected, the plasma protein was lowered as the former rose. In an analysis of the paired animals, that is, comparing those animals treated with pressure dressings versus those animals without dressings, several generalizations can be made: In practically all instances the degree of hemoconcentration was greater in the animal without a dressing than those which received pressure over and around the site of injury. An-

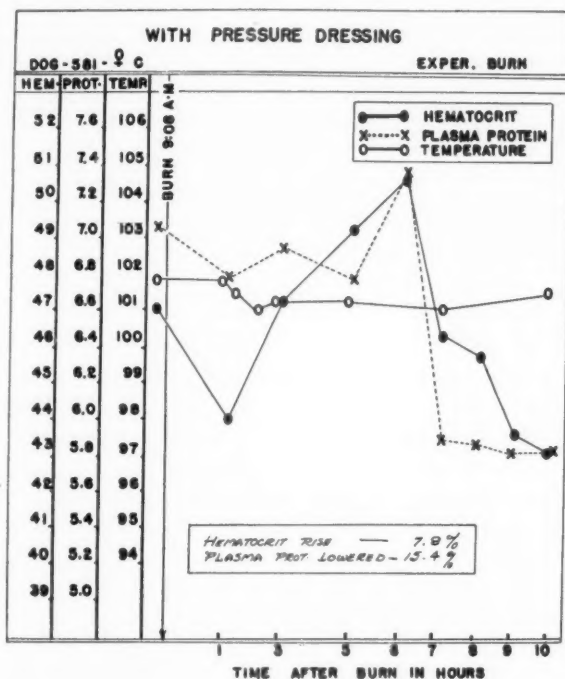


CHART 2.—Representative graph of hematocrit and plasma protein observations in an animal with a pressure dressing over the burned area.

other interesting fact is that the rate of hemoconcentration occurred more rapidly in the group without a pressure dressing. The maximum point of hemoconcentration was reached usually two to three hours after sustaining the burn. A representative example is shown in Chart 1. In the group of animals with pressure dressings the rate of hemoconcentration was slower, with the maximum point usually observed four to six hours after the injury (Chart 2). These observations suggest to us that pressure over and around the site of injury mechanically suppresses the rate of plasma loss.

A more careful study of the two composite groups was done. To submit the results to biomathematical analyses we felt that it was more just to use

the percentage change in the hematocrit determinations of the two groups rather than the actual figurative change. The method of statistical analysis used was the "t-test" of Student.⁷ In this test "t" is the difference between two means divided by the standard error of that difference. On analysis (Table IV), it is revealed that such a change in the hemoconcentration,

TABLE IV
STATISTICAL ANALYSIS OF THE MAXIMUM HEMATOCRIT CHANGE IN EXPERIMENTAL BURNS

Burns Without Pressure			Burns With Pressure		
Pair No.	% Diff.	(% Diff.) ²	Pair No.	% Diff.	(% Diff.) ²
1	28.3	801.0	1	18.9	355.8
2	17.2	296.7	2	2.3	5.4
3	3.6	13.2	3	15.4	238.5
4	5.5	30.2	4	0.2	0.04
5	34.5	1187.4	5	17.9	320.9
6	16.9	284.7	6	3.7	14.0
6	105.9	2613.1	6	58.5	934.7
Mean %			Mean %		
17.6			9.7		
S=10.5		t=1.304	P=0.2		

The significance of these observations was determined by use of the formula devised by Student.

observed with and without pressure, could occur 20 in 100 times, due to chance alone. To be significant it must be five or less times in 100, due to chance. This assay does reveal that the pattern of response is more regular in those burned animals with pressure dressings than those without pressure.

Other observations suggest that the dogs with pressure dressings suffered much less "thermal shock" than those without dressings. In the former group the temperature generally did not go so high, and the pulse rate did not show the degree of increase as did those dogs in the latter group. Furthermore, we observed that the dogs with pressure dressings appeared to be more comfortable, generally, than the dogs without dressings. The tendency was for them to move about and take fluids without a great deal of discomfort.

There are some very definite reasons why we are not attempting to analyze and discuss the degree of hypoproteinemia in this experiment. In the first place the exact mechanism of balance between the protein content of the blood and of the tissue is not too well understood at this time. Moreover, as plasma protein is lost the mechanism of drawing upon protein reserve of the tissue is not known, and until further investigation clarifies this phenomenon we must be satisfied to accept protein determinations at face value, that is, that the protein determination represents the amount present in the circulating plasma when the sample is withdrawn.

These animal experimentations suggest that pressure on and about a burned area may inhibit the rate and degree at which hemoconcentration occurs, but do not conclusively prove it. We realize that a great many factors enter into this problem and that more research must be done before

definite conclusions can be reached. Some phases of this study are now being done.

Discussion.—In the untreated burns hemoconcentration was obtained on an average of two to three hours after the injury, while in the dogs where a pressure dressing was applied it occurred on an average of four to six hours after the injury.

The mean per cent of hemoconcentration was 17.6 in the untreated animals, and 9.7 per cent in the animals with pressure dressings. This average per cent difference would suggest that pressure on and about a burned area is beneficial in preventing hemoconcentration, yet on statistical analysis it is not significant.

The circulating plasma protein was lowered in about the same ratio as hemoconcentration occurred. As stated elsewhere, we have not attempted to analyze this change since the relationship between circulating plasma protein and the protein reserve in the tissues is not known and apparently variable.

CONCLUSIONS

(1) Our clinical and experimental studies suggest that primary pressure dressings may reduce the loss of plasma at the site of, and into the surrounding tissues of, burned areas.

(2) The capillary hematocrit method was used for determining the hemoconcentration in both patients and animals. It is very rapid, requires much less blood, and is, we believe, more accurate than other methods generally employed.

(3) With this form of dressing, hemoconcentration may be delayed and perhaps is less severe.

(4) The drop in plasma proteins was definitely less in the dogs treated by pressure dressings than it was in the controlled animals. The significance of this may be open to question, inasmuch as the balance between the tissue proteins and the circulating proteins is not well understood.

(5) It appears to us that the pathologic-physiologic changes resulting from burns is less severe and more readily controllable under this form of therapy than by other methods employed. Certainly the patients are more comfortable and more easily cared for. The incidence of infection has been relatively slight.

(6) What effect the use of sulfonamides in the treatment of burns will have, systemically and locally, in addition to the procedures described, has not yet been determined. It appears certain that they will aid materially in further controlling the infection.

(7) In conjunction with cleansing and débridement of the burned area we have used the method of primary pressure dressings, as described in this paper, upon 134 patients. The mortality rate was 3.7 per cent.

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DISCUSSION.—DR. WILDER G. PENFIELD (Montreal, Canada): I want simply to call attention to the fact that the subject of burns is a most timely one at the moment. During the last Autumn I had the opportunity to go to Great Britain to make some sort of survey of clinical surgical problems there for the Canadian Research Council, and during that trip I had the opportunity of being in the general hospitals and in the military hospitals, British and Canadian.

My own reaction to the clinical problems was that burns are the outstandingly important problems. There are a good many burns now, of course, because of the fact that there are burns from bombs, because very frequently in open fireplaces the contents of the fireplaces are driven out into the faces of people sitting about them, because of the use of incendiary bombs, and because of flash burns on all the surfaces. But it seems quite likely that all of the surprises that are to be sprung in this war have not yet appeared. It is possible that the forces may be called upon to deal with chemical burns, to deal with flame burns of a different type, and the need of surgeons who have the material in their hands of voluntarily directing their attention to this problem is a great one. The simple problem of early recognition of a third-degree burn, the question of whether tanning increases the depth of the initial burn, the problem of the control of pain, and of course, the problems of shock, infection, toxemia, scarring, wound healing, all come into the picture. But what is needed is not a council of perfection in the treatment of burns. What is needed is standardized, simple methods which could be used by a man in a dressing station who has 5 or 50 burns to treat at once, methods that can be used in hospitals that might have to treat hundreds of them.

DR. SUMNER L. KOCH (Chicago, Ill.): I am delighted to have an opportunity to hear these papers, because it seems to me never has a presentation been made that has stressed so clearly and emphatically the application of sound surgical principles to the treatment of a difficult problem. Doctors Siler and Reid have done that. They have emphasized, first of all, the careful cleansing of the open wound without adding further contamination and further infection; second, the application of a dressing that does not add injury, that does not cause a further destruction in addition to that which has been sustained; third, the value of pressure, a factor in wound healing which was emphasized years ago by Doctor Blair, which was forgotten, remembered, and now is being utilized to help wound healing; fourth, Doctor Siler has suggested limiting the important fluid loss; and fifth, putting the part at rest.

These are sound surgical principles. They are going to live if they are sound, and it seems to us they are definitely applicable.

We have been using that method at the Children's Hospital, the Cook County Hospital, and for a period of three years, beginning January 1, 1939, we have used the method exclusively. During that period of time, with the help of Dr. Harvey Allen, who is now at Camp Custer, and of some splendid residents who are now in the Army and Navy, we were able to care for 485 hospitalized cases with severe burns. The mortality in that group was 19 cases, or 3.9 per cent, a little higher than the mortality that Doctor Siler and Doctor Reid have. And all the other things that could be said concerning the ease of care, the lessening of hospital morbidity, etc., were observed in these cases also.

Now, without wishing for a moment to answer for Doctor Siler or Doctor Reid the question that Doctor Penfield suggested, we had a discussion in Chicago on this problem of burns, and Captain Cook said: "Well, that method might work splendidly in a hospital where you have every help and available resources. It will not work at all

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in the field." We tried to say that the method, or something analogous to it, would work. If men were simply instructed, first of all, to mask themselves and not add infection, and then to put a preparation, an exact preparation we will not pretend to describe, over these open wounds, consisting of an oily dressing containing a sulfonamide, such as Doctor Dragstedt, and his associates, used at the University of Chicago. Then over this dressing, which could be applied with sterile spatula very rapidly, a compression dressing and a splint were applied, it seemed to us that such a method might be used in a large group of cases, and thus be made fit for transportation. When the opportunity arose, they could be treated by this more definitive method of treatment that Doctor Siler has described so well.

DR. LEO ELOESSER (San Francisco, Calif.): This discussion has centered largely upon variations on an old theme, namely, the variations in the various applications of antiseptics. I wonder whether in third-degree burns, leaving quite aside the first- and second-degree burns, we are not standing still as we were standing in the era before the débridement of wounds. The question that Doctor Penfield has brought up is very important—could something be done for third-degree burns where they are not received in too great numbers, especially for burns of the face and hands, as it is to other wounds, namely, an early débridement and an attempt to convert what is certain to become a more or less septic wound into a surgically aseptic wound. I think perhaps if we could débride earlier wound lesions, especially of the hands and face, and immediately skin graft these surfaces we know are doomed to destruction, perhaps the complications which we have been discussing this morning might be avoided.

I merely put that question to you for your consideration. I think that in a few cases those methods are applicable. As Doctor Penfield says, when many of them are received at once, the method is too time-consuming to be used widely, but where not many of them are received, then I think it is useful.

DR. VINTON E. SILER (closing): Apropos of Doctor Young's talk, I would like to say that we have not proposed this. I am sure Doctor Koch has the ideal method. It may be just the compromise between the simple procedure and the ideal.



SCIENCE AND HUMAN PROGRESS—III

Entomology and Survival

ENTOMOLOGY, devoted to the study of insect life, has already greatly aided humanity to win the bitter struggle against the vast hordes of insects competing for our food supply. A most striking illustration of the effective work of entomologists is the recovery of the continent of Australia from threatened depopulation by the swift spread of a fast-growing cactus. A million acres of valuable land were being occupied annually by cacti in an advancing wave no ordinary measure would stop. The entire continent was in danger of being engulfed, as sixty million acres had been, when entomologists suggested employing an insect which lives only on cactus plants. The *Cactoblastis cactorum* was finally brought in from Central America and by virtue of its prodigious appetite and enormous fecundity Australia has been saved for Man.

—A. Cressy Morrison, Transactions of the New York Academy of Sciences, Series II, 2, No. 3, January, 1940.

INFECTED BURNS WITH HEMORRHAGE*

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OCCASIONALLY chronically infected burns show a decided bleeding tendency which seems to resist all forms of topical and general therapy. Although infection is a common complication of cutaneous burns, hemorrhage is relatively rare, occurring in approximately 2 per cent of the cases.¹ Gunn and Hillsman² state that hemorrhage occurs in only a small percentage of cases, and is usually met with only in dirty, sloughing, badly infected burns. Da-Costa³ mentions that the raw surface, resulting from separation of sloughs in deep burns, is slow to heal, and may be complicated by hemorrhage.

If the infected burned area is extensive, the prolonged and uncontrolled bleeding results in a major therapeutic problem. The constant loss of blood soon produces a marked anemia and subnormal serum protein level, in spite of frequent blood transfusions. The absorption of septic bacterial products causes a continued septic fever with frequent chills, rapid pulse, prostration, and increasing debility. The patient's mental depression and the marked tendency to develop contractures further complicate an already difficult problem. A vicious cycle becomes established—the more the patient bleeds, the greater the infection becomes as a result of the anemia, low plasma proteins and debility; and the greater the infection becomes, the more the patient bleeds.

In the three cases of chronically infected burns which we are reporting, the bleeding was characterized by a continuous diffuse ooze of blood over long periods of time, up to five or six months. The local use of lanolin or vaselined pressure dressings and various topical applications of such solutions as boric acid, Burow's, Dakin's, azochloramide, dilute acetic acid, mercurochrome, hydrogen peroxide, silver nitrate, and 1 per cent copper sulphate failed to bring the bleeding under control. The administration of sulfonamides orally in two, and locally in one of these patients, was likewise unsuccessful. In each instance, however, the application of a water suspension of activated zinc peroxide dramatically stopped bleeding within 24 to 48 hours.

CASE REPORTS

Case 1.—Our attention was first attracted by this hemorrhagic tendency in the case of R. C., white, male, age 24, who was admitted to the Holmes Hospital, November 22, 1940, with an old infected electrical burn of his back of six years' duration. The infection was chronic and recurred frequently in spite of repeated radical excisions and many types of treatment. At the time of this admission, an ulceration three inches in diameter was present in the burn scar over the center of the lower back. The infected granulation tissue exhibited a persistent bleeding tendency which previously had

* Read before the American Surgical Association, Cleveland, Ohio, April 6-8, 1942.

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not been controlled by Dakin's, azochloramide, copper sulphate, saline, boric acid, hydrogen peroxide or specific bacteriophage solution locally. Lugol's solution and sulfanilamide by mouth also were ineffective. His red blood count progressively fell to a level of 2,800,000, with a hemoglobin of 9 Gm. His bleeding time, blood platelet count and prothrombin time were all within normal limits.

Bacteriologic study of the wound showed presence of an aerobic hemolytic staphylococcus and an anaerobic nonhemolytic streptococcus. It was thought that this case probably represented a type of chronic cutaneous ulceration, as described by Meleney. Caustery excision of the infected area followed by daily dressings with zinc peroxide was done, and the bleeding was promptly controlled. As soon as the zinc peroxide was discontinued and another solution, such as Dakin's, was employed, the bleeding promptly reappeared. The reapplication of zinc peroxide again quickly stopped the loss of blood.

After the effective control of the infection and bleeding, the clean granulating area was then successfully grafted by means of pinch-grafts followed in 12 hours by continuous zinc peroxide dressings. The patient was discharged March 3, 1941.

Case 2.—T. R., white, male, age 48, received second- and third-degree burns of the legs, thighs, arms, and hands, November 2, 1940. While using an acetylene torch to cut metal, a can of gasoline nearby became ignited, which, in turn, ignited the patient's clothing. He was admitted to the Dermatologic Service of the Cincinnati General Hospital one hour after injury. Treatment consisted essentially of continuous dressings of Burrow's solution, bed rest, and general supportive measures. Fifteen days later, it was noted that the patient had developed infection of the burned areas.

When he was transferred to the General Surgical Service for treatment and grafting, December 3, 1940, it was noted that the burned areas on both legs were bleeding. After continuous compresses with Dakin's solution, postage stamp Thiersch grafts were applied to the granulating wound. The grafted areas soon broke down and the wounds continued to bleed. Many types of topical therapy were then tried but all failed to stop the bleeding. Among the solutions used were saline, boric acid, acetic acid, azochloramide, cephrin chloride, mercurochrome, Dakin's solution and hydrogen peroxide. In spite of frequent blood transfusions, the anemia became more and more pronounced. He received daily 24 ounces of orange juice and 75 mg. of cevitamic acid, without influence on the bleeding.

On April 10, 1941, the patient was shown in surgical ward rounds, and at that time he appeared obviously and chronically ill. The burned areas on both legs were covered with large masses of dark partially clotted blood and pus beneath which the granulation tissue was piled up and edematous (Fig. 1 A). Active continuous oozing of dark blood could be seen.

The patient was debilitated, discouraged, and disfigured by contractures of both legs. The temperature was 100–102° F., and of the septic type; pulse 100–130. *Laboratory Data:* R.B.C. 2,300,000; hemoglobin 8 Gm.; serum protein 5.7 Gm. per cent; serum albumen 2.5 Gm. per cent; serum globulin 2.2 Gm. per cent; hematocrit 31 per cent. The prothrombin time was 93 per cent and the blood platelet count was 260,000. After four and one-half months of unsuccessful effort to control the bleeding, the loss of blood became so alarming that bilateral amputation of the affected legs was strongly considered as a last resort.

Careful cultures of the wounds at that time revealed the presence of nonhemolytic *Staphylococcus albus*, hemolytic *Staphylococcus aureus*, and a nonhemolytic streptococcus. No strictly anaerobic bacterium was demonstrated.

On the basis of our experience in the former case, the local use of zinc peroxide seemed indicated, even though no strictly anaerobic or micro-aerophilic bacteria were present. In addition, the legs were straightened and slightly elevated by means of traction applied to Steinmann pins inserted through the os calcis.

Twenty-four hours after the first application of zinc peroxide suspension the bleeding was completely stopped (Fig. 1 B), and the granulation tissue was beginning to assume a bright red, healthy appearance, which became more pronounced daily. Multiple whole-

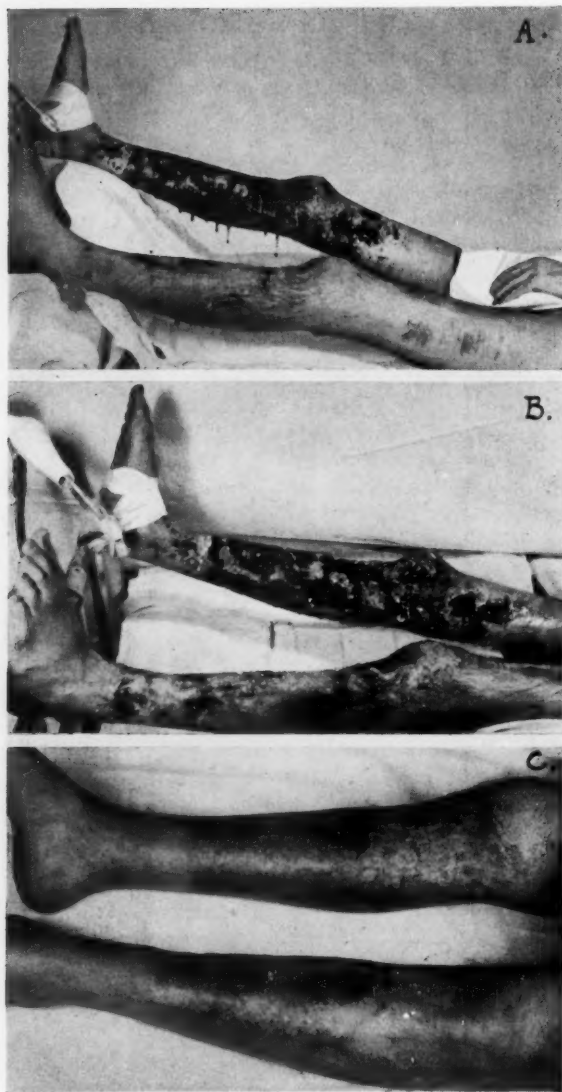


FIG. 1.—A. Bleeding granulation of infected burn of Case 2. B. Appearance of granulation tissue 24 hours after first application of zinc peroxide suspension showing complete arrest of bleeding. C. Same wounds after skin-grafting and healing.

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blood transfusions were given, and within two weeks the patient looked much improved; his R.B.C. was then 4,000,000, and his temperature had fallen to approximately normal. The wounds were pinch-grafted in five sittings, between the dates of May 1, 1941 and

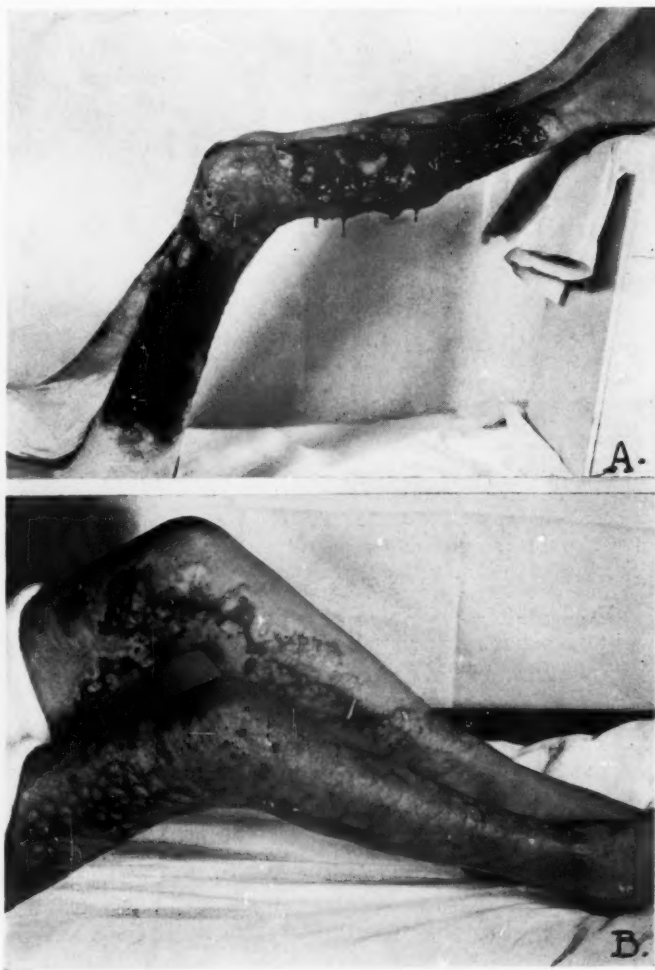


FIG. 2.—A. Bleeding granulation tissue of infected burn in Case 3. B. Same wounds after skin-grafting and healing.

July 15, 1941, because of the extent of the involved areas. By August 25, 1941 all wounds were healed except several small crusts, and only at this time was zinc peroxide therapy stopped. He was discharged November 1, 1941, completely healed (Fig. 1 C).

Case 3.—M. L., white, male, age 13, was admitted to the Children's Hospital, June 13, 1941, 17 days after having received second- and third-degree burns of both lower extremities and his right forearm. While playing with a small fire, gasoline was thrown by him into the fire. The ignited fuel exploded on his trouser legs, and in removing these, he burned his right forearm. He was carried immediately to another hospital where the wounds were cleaned and sprayed with tannic acid. During the first week infection occurred beneath the eschar and it was, therefore, necessary to remove a great part of the crust. Warm saline compresses were then applied. At this time he

was seen and treated on the Surgical Service of the Children's Hospital. His temperature was 105° F., and of the septic type. Urinalysis was essentially negative. R.B.C. 3,560,000, hemoglobin 9.1 Gm. per cent. The wounds were treated with warm saline compresses followed in three days with Dakin's solution. The granulations rapidly attained a healthy appearance, but the patient still ran a septic course. The wounds were grafted June 24, 1941, July 17, 1941, and August 7, 1941. By September 7, 1941, 30 days after the last grafting, the granulations were bleeding quite freely and piling-up thickly about the now disappearing grafted skin. A donor area from the left thigh reacted similarly, being obviously infected. The patient was very pale, discouraged and disfigured by flexion contractures and large bleeding infected wounds of both legs (Fig. 2 A). R.B.C. 3,100,000, hemoglobin 7.4 Gm. per cent, hematocrit 23 per cent. Many solutions were used unsuccessfully, including acetic acid, saline, boric acid, azochloramide in olive oil and lanolin pressure dressings. Multiple blood transfusions were given and he was placed on a diet rich in vitamins. On September 18, 1941, when the patient was first seen by us in consultation, a hemolytic *Staphylococcus aureus*, hemolytic streptococcus, and a hemolytic *B. coli* were cultured from the bleeding and infected wounds. The following day applications of zinc peroxide suspension were started; and the previously hemorrhagic, dark red infected granulation tissue became healthy appearing and bloodless in less than 48 hours. Within 14 days the granulations had become flat and pinch-grafts were successfully applied September 25, 1941 and October 6, 1941. The application of zinc peroxide was resumed 12 hours after the grafting. Except for a few small granulating areas the wounds were completely epithelized by October 19, 1941, and the zinc peroxide dressings were then discontinued. Straight leg traction and exercises overcame the flexion contractures of his legs.

Except for a short vacation during the holiday season he remained hospitalized until March 15, 1942, at which time the legs were completely epithelized. (Fig. 2 B.)

Discussion: In each of these three cases the complication of bleeding was very serious, and always associated with chronic infection, but never with jaundice, low prothrombin time, or other obvious manifestations of liver deficiency. This type of bleeding, developing spontaneously during the granulating stage, is not to be confused with that occurring earlier, either due to depressed blood prothrombin levels^{1, 5} or separation of large infected sloughs. The cause of the bleeding tendency and the explanation of the effectiveness of zinc peroxide are obscure. According to Harkins,⁵ hemorrhage from superficial vessels may occur either during sloughing or later in the granulating stage of burns. There is considerable evidence that some bacterial product produces the bleeding. The constant association of this complication with infection, as noted by Gunn and Hillsman,² and as demonstrated by our cases, supports this view. The continued oozing of blood indicates that the hemorrhage is of the capillary type, which, occasionally, may be the result of damage to the capillaries by bacterial toxins.⁶ Likewise, the rapid arrest of the bleeding, coincident with the control of the infection by zinc peroxide, strongly suggests that its bactericidal and detoxifying action are responsible for its effectiveness.

Although zinc peroxide is usually considered to be indicated in lesions contaminated or infected by anaerobic or micro-aerophilic bacteria, Johnson and Meleney⁷ have demonstrated that this substance also possesses a bactericidal action *in vitro* for hemolytic streptococci and pneumococci, and a detoxifying or destructive action on the hemotoxins of the streptococcus and gas bacillus. As relatively resistant to the action of zinc peroxide they

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listed the staphylococcus, *B. coli*, *B. pyocyaneus*, and *B. proteus*. We have been able to show a similar destruction of the hemolysin of the staphylococcus and of the *B. coli* as well as the streptococcus after incubation for half an hour with zinc peroxide.

A study of the bacteria isolated from each case shows that the great majority were hemolytic varieties, and that the hemolytic *Staphylococcus aureus* was the only one common to each case (Table I).

TABLE I

BACTERIA ISOLATED FROM BLEEDING BURNS

1. R. C.—Hemolytic *Staphylococcus aureus*.
Nonhemolytic *Staphylococcus aureus*.
Nonhemolytic anaerobic streptococcus.
2. T. R.—Hemolytic *Staphylococcus aureus*.
Streptococcus fecalis.
Nonhemolytic *Staphylococcus albus*.
3. M. L.—Hemolytic *Staphylococcus aureus*.
Hemolytic streptococcus.
Hemolytic *B. coli*.

Certain strains of the *Staphylococcus aureus* may produce a variety of toxic substances in artificial culture media, including hemolysin, leukocidin, necrotizing toxin, lethal toxin, gastro-enteric toxin, plasma coagulase, and fibrinolysin. We have found no reference to the ability of staphylococcal toxins to cause hemorrhage; in fact, plasma coagulase supposedly favors septic thrombosis in staphylococcal infections. It is possible that this organism produces an additional toxic factor which is responsible for this type of bleeding.

Attempts to produce capillary hemorrhage from granulating surfaces of burns in dogs by the injection or continuous application of bacterial free filtrates rich in staphylococcal, streptococcal, and *B. coli* hemolysins have failed.

SUMMARY: Three cases of chronically infected burns are presented in which a late and serious complication was continuous capillary bleeding. After many types of local therapy had failed, the application of zinc peroxide immediately stopped the bleeding. If the zinc peroxide was discontinued, the bleeding recurred within a few days. Reapplication of the zinc peroxide again quickly controlled it. The nature of the bleeding and the action of the zinc peroxide remain unexplained.

CONCLUSIONS

In conclusion we wish to emphasize the following points in the management of these and similar cases:

- (1) The prevention of this or other types of infection by careful débridement and cleansing of the freshly burned area.
- (2) The advantage of careful bacteriologic cultures.
- (3) The effectiveness of zinc peroxide dressings in the control of this type of bleeding as well as of the infection.
- (4) The prevention of contractures.

- (5) Adequate blood transfusion to restore the red blood corpuscles and hemoglobin to normal levels.
- (6) Skin grafting as early as possible.
- (7) Reapplication of zinc peroxide within 12 hours after grafting.

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DISCUSSION.—DR. FRANK L. MELENEY (New York): I wish to say just a few words about Doctor Altemeier's paper, which interested me a great deal. We have had similar experiences in bleeding from chronically infected wounds when using zinc peroxide, with cessation of bleeding, but they were not quite so dramatic as the cases which he has presented.

It will be remembered that the chronic, undermining, burrowing type of ulcer, in which the value of zinc peroxide was first demonstrated, previous to that demonstration was very frequently associated with a profuse hemorrhage, and even fatal hemorrhage when there was erosion of some large blood vessel. Further than that, however, in some of the chronic cases, one of which Dr. Sumner Koch will remember, even without serious bleeding there was frequently a very rapidly developing anemia which could only be controlled by transfusions. However, with the use of zinc peroxide in that particular case the first result was the rise in hemoglobin and red cells, and the end of the necessity of transfusion, so that besides the immediate action on the surface blood vessels and on the deep blood vessels, there is another hemolytic action which is probably generally absorbed into the blood stream and acts upon the blood-forming organ.

I believe that these cases represent secondary hemorrhage, similar to that which we have all seen in our experience from continuous severe infection.

As Doctor Altemeier has said, we demonstrated the effect of zinc peroxide on the growth organisms *in vitro*, and we found that the action was most striking upon those which were most highly anaerobic, but the action was also present, at least bacteriostatic if not bactericidal, on the micro-aerophilic organisms and certain of the aerobic organisms.

The experiments were done first with very high dilutions of zinc peroxide (half of 1 per cent) which showed the lethal action on anaerobic or micro-aerophilic organisms, and required 1 per cent, 5 per cent, and even to 20 per cent to be bacteriostatic on the aerobes. That was demonstrated on the hemolytic *Staphylococcus aureus*. I think that Doctor Altemeier, if he still has those cultures, might attempt to demonstrate the bacteriostatic action upon the organisms which were found in these cases, not only in pure culture but in mixed culture, because it is known that organisms in skin biopsies will often have an action which they cannot produce in pure culture.

DR. WILLIAM A. ALTEMEIER (closing): I want simply to mention that we have seen two additional cases of burns which have had this bleeding tendency, but which were lesser in degree and which, of course, we have not included in the report.

Doctor Meleney has asked me to state that there are eight units that have been set up throughout the country under the auspices of the National Research Council for the study of contaminated wounds and burns, and that during the coming year we hope to answer many of these problems that have been discussed.

**A SIMPLE METHOD FOR ESTIMATING PLASMA PROTEIN
DEFICIT AFTER SEVERE BURNS ***

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THOUGH the importance of plasma transfusions in the treatment of burn shock is now generally accepted, there is less agreement in regard to the amount of plasma to be given, and the timing of its administration. Increasing experience indicates that it is difficult to set up a "rule-of-thumb" which will cover even a majority of the requirements of all patients, and that plasma dosage is an individual problem which varies with each patient.

That there is a need for a simple and accurate method for determining plasma loss caused by burns is evidenced by the many methods which already have been suggested.^{1, 2, 3, 4, 5} The formula offered by the authors in a previous contribution¹ meets one of these requirements, namely, accuracy, but it lacks the virtue of simplicity. Further experience has shown that to be practical for general use such a formula should require but a minimum of laboratory data and mathematical calculations. We, therefore, offer as a key to the use of our formula a chart from which the plasma protein deficit may be read directly if the hematocrit or hemoglobin level, plasma protein level, and body weight are known.

This paper will present the chart, describe its use and also give a derivation of the authors' equations for calculating plasma protein deficits resulting from severe burns.

A CHART OF PROTEIN DEFICITS AFTER BURNS

In order to simplify the calculation of protein losses resulting from severe burns values were calculated from the authors' equation¹ for the average adult with a normal hematocrit of 45 per cent cells, and a body weight of 70 Kg. (154 lb.). The calculated protein deficit, in grams, was plotted against the assumed hematocrit values for several plasma protein levels as shown in Chart I. Hematocrit values are represented by points on the horizontal base line, plasma protein deficits or equivalent plasma volumes by points on the vertical margins, and plasma protein concentrations by the curves. Therefore, each vertical line in the chart represents a given hematocrit value and each horizontal line a plasma deficit. To read the deficit for a burned patient, take the point where the vertical line corresponding to the observed hematocrit value intersects the curve corresponding to the estimated plasma protein level, interpolating whenever necessary. The horizontal line

* Read before the New York Surgical Society, New York, N. Y., March 11, 1942.

from this point to the left margin of the chart indicates the plasma protein deficit, in grams, and to the right the equivalent volume of normal plasma. If the weight of the patient differs markedly from 70 Kg., for which the calculations were made, the deficit read from the chart must be multiplied by a suitable factor. An example is given on the chart. If only the hematocrit can be determined the protein level is assumed as 6.0 to 7.0 Gm./100 cc. during the first 48 hours following the burn, provided the total intake of fluids is restricted to three liters per day. It should be pointed out that large errors may be introduced if the protein level is unknown. In the uncontrolled burn case the protein level may vary between wide limits.

Hemoglobin levels equivalent to each hematocrit value may be substituted on the horizontal axis. This can be done because the chart defines the relationship of hemoconcentration to plasma protein loss caused by severe burns. The limitations of this procedure will be discussed below.

The chart cannot be used directly for burned cases complicated by hemorrhage, anemia or polycythemia. The anemic individual, especially a child, presents a problem not easily handled by any chart or fixed rules. A whole series of charts, one for each basal hematocrit, is needed for the entire range of anemias. The chart may be used if due allowances are made for the degree of anemia. At the same hematocrit level the plasma deficit for an anemic individual is 20 to 100 per cent greater than that for a person with a normal hematocrit. Therefore, values from the chart are minimal and must be increased proportionally for the anemic patient. This is also true for the burned patient who has lost red cells by hemorrhage. In the patient with polycythemia the protein deficit is considerably less than the value indicated by the chart. Allowances must be made for added red cells if a whole-blood transfusion is given. In all of these instances the most dependable value for the protein deficit is obtained by substituting probable normals in the formula derived below and calculating.

DERIVATION OF THE EQUATIONS

The calculation of plasma volume changes and protein deficits is based on several assumptions which do not meet the rigid requirements for laboratory research data but are sufficiently valid for clinical use. Normal plasma volume, in liters, is taken as 5 per cent of the body weight in kilograms ($0.05 \times W$). Normal plasma protein level is assumed to be 7.0 Gm. per 100 cc. Hence, total circulating plasma protein is $0.05 \times W \times 7.0 \times 10 = 3.5W$. The change in plasma volume for a unit indicated by changes in serial hematocrit values may be taken as representative of the entire plasma volume. It is further assumed that the total volume of cells in the vascular tree does not change significantly during a series of observations considered here. The equations cannot apply if there has been any marked change in red cell volume through hemorrhage, either external or internal, transfusions of whole blood or osmotic shifts of water. If the cell volume under normal conditions = H_n per cent by volume of whole blood, then $100 - H_n = cc.$

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CALCULATED PLASMA PROTEIN DEFICIT IN SEVERE BURNS

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ANNALS of SURGERY

J. S. LIPPINCOTT CO., PHILA., PA.

$$\text{Grams Protein} = 3.5 W - \frac{W(100 - H_o)H_n Po}{2(100 - H_n)H_o}$$

$W = 70 \text{ Kg.}, \text{ Body Weight}$

$H_n = 45 \% \text{ Cells, Hematocrit}$

$H_o = \% \text{ Cells Shown in Graph}$

$Po = \text{Protein Levels Shown in Graph}$

PLASMA PROTEIN
DEFICIT

Gm.
240

220

200

180

160

DEFICIT as VOLUME
NORMAL PLASMA
Ml. or Cc

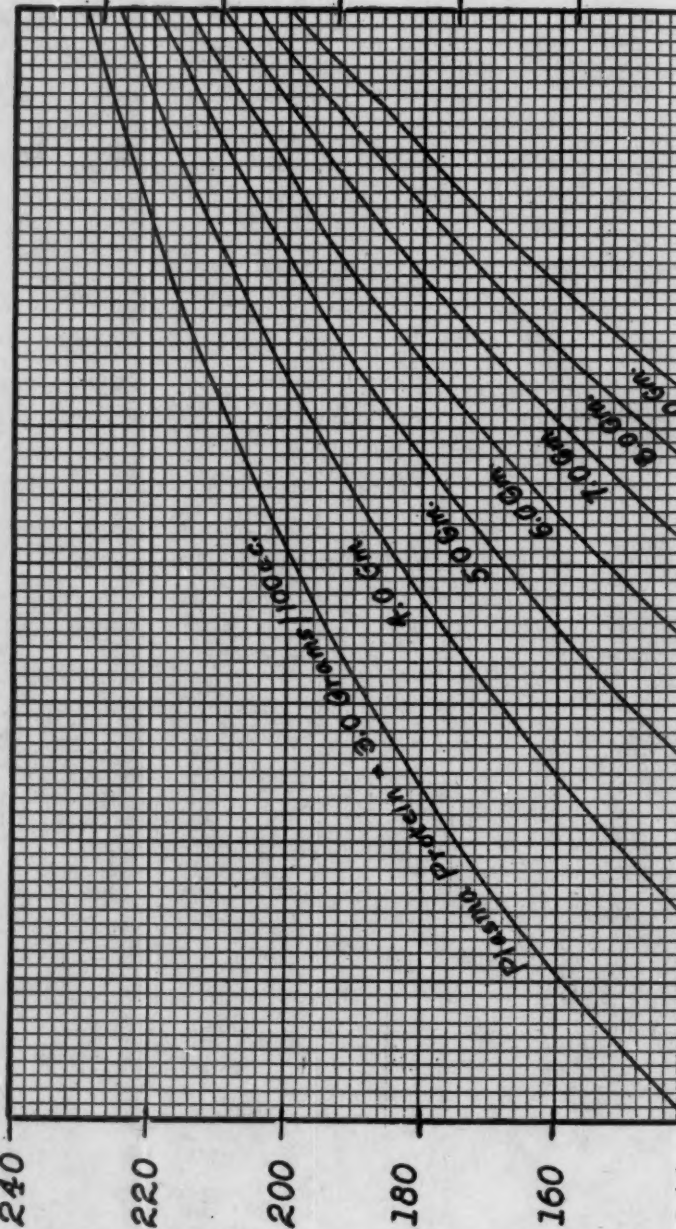
3250

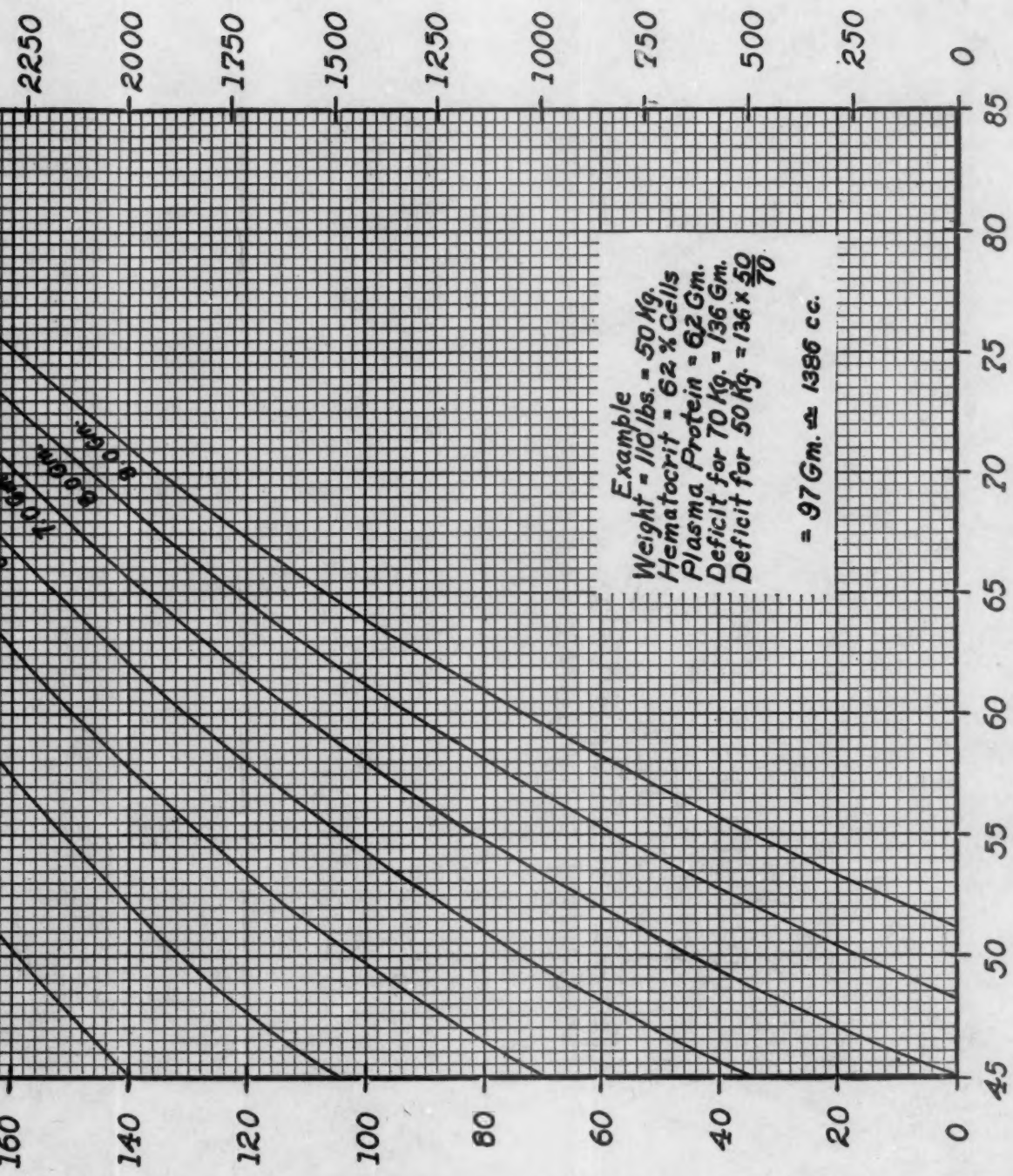
3000

2750

2500

2250





H₀ = OBSERVED HEMATOCRIT

CHART I

ESTIMATION OF PLASMA PROTEIN

plasma per 100 cc. whole blood. Also, unit volume of plasma per unit volume of cells will be:

$$\frac{\text{Plasma}}{\text{Cells}} = \frac{100 - H_n}{H_n}$$

In like manner, when the plasma volume is suddenly changed by extravasation of plasma (or by dilution) without appreciable change in cell volume, the new cell volume is designated as H_o per cent by volume of cells in whole-blood, and $100 - H_o =$ cc. plasma per 100 cc. whole-blood. The plasma volume per unit volume of cells is:

$$\frac{\text{Plasma}}{\text{Cells}} = \frac{100 - H_o}{H_o}$$

Since unit cell volume is the same in both instances the ratio of the second plasma volume to the normal volume may be written:

$$\frac{\frac{100 - H_o}{H_o}}{\frac{100 - H_n}{H_n}} = \frac{(100 - H_o)H_n}{(100 - H_n)H_o}$$

This ratio multiplied by the initial plasma volume ($0.05W$) gives the calculated plasma volume at any given value for H_o .

Plasma volume at hematocrit:

$$H_o = \frac{(100 - H_o)H_n 0.05W}{(100 - H_n)H_o}$$

If the concentration of protein in the altered plasma volume is P_o Gm. per 100 cc. the total quantity of circulating protein is:

$$\frac{(100 - H_o)H_n 0.05W \times P_o \times 10}{(100 - H_n)H_o}$$

The protein deficit is the initial plasma protein less this value or: Protein deficit in grams equals:

$$3.5W - \frac{W(100 - H_o)H_n P_o}{2(100 - H_n)H_o}$$

The terms may be redefined:

W = Body weight in kilograms.

H_n = Normal hematocrit,* per cent cells.

H_o = Hematocrit* per cent cells, after the burn.

P_o = Plasma protein, Gm./100 cc., after the burn.

In similar manner accurately determined hemoglobin levels may be used to express plasma loss because there is a remarkable constancy in the size and hemoglobin content of the red cell in normal persons.^{6, 7} The content

* The total cell volume rather than the usual hematocrit value gives more accurate results when there is a marked leukocytosis.

of hemoglobin in blood is, therefore, proportional to the total volume of red cells or the hematocrit value. Obviously, the volume of plasma is the difference between the total blood volume and the cell volume. The calculation is made in this manner: Let K = Grams hemoglobin in 100 cc. packed cells. Let Hb_n = Grams hemoglobin in 100 cc. normal blood. Let Hb_o = Grams hemoglobin in 100 cc. whole-blood which, through changes in plasma volume only, has more or less hemoglobin than the normal level. Then $K - Hb_n$ is a measure of normal plasma volume, while $K - Hb_o$ is a measure of the altered plasma volume after the burn. From this point the derivation is identical with that of the hematocrit plasma protein equation presented above. The final equation takes the form: Protein deficit in grams equals:

$$3.5W - \frac{W(K - Hb_o)Hb_nP_o}{2(K - Hb_n)Hb_o}$$

Key: W = Body weight in kilograms.
 K = Gm. hemoglobin in 100 cc. packed cells.
 Hb_n = Gm. hemoglobin in 100 cc. normal blood.
 Hb_o = Gm. hemoglobin in 100 cc. blood after the burn.
 P_o = Gm. protein/100 cc. plasma

This equation, relating plasma volume changes to hemoglobin levels, gives the same calculated deficits shown by Chart 1. The equivalent hemoglobin level is substituted for each hematocrit figure on the horizontal axis. Such equivalents, calculated from Haden's normals, are shown in Table I. Similar equivalents may be calculated for the normals established in any other laboratory.

TABLE I
EQUIVALENTS CALCULATED FROM HADEN'S NORMALS

Hematocrit % Cells	Hemoglobin Gm./100	Hemoglobin % Normal
45.0	15.40	100
47.5	16.25	106
50.0	17.10	111
52.5	17.96	116
55.0	18.82	122
57.5	19.67	128
60.0	20.53	134
62.5	21.40	139
65.0	22.25	144
67.5	23.10	150
70.0	23.98	156
72.5	24.82	161
75.0	25.70	167
77.5	26.54	172
80.0	27.40	178

Two serious difficulties arise in using hemoglobin levels for estimating plasma volume changes. The error in hemoglobin determinations, by the widely used methods, is entirely too large for the present purpose. The gasometric methods are quite accurate but are not suitable for routine use,

but hemoglobin levels, determined as oxyhemoglobin, with an accurately calibrated photoelectric colorimeter, are quite reliable and may be used whenever available. In the second place, a marked leukocytosis (usually seen in severe burns) causes a discrepancy between the total cell volume and the hemoglobin level. This disparity is increased by a swelling of the red cells following a hemorrhage, as observed by Brennan.⁸ For these, and other reasons, the hematocrit is the method of choice in following burned patients.

The above equation represents a general type of expression which may be modified to show a variety of relationships. In a previous publication,⁹ the same mathematical reasoning was used to express the total base changes in extracellular fluid. The validity of this reasoning depends on (1) the accuracy of assumed normal values; (2) the constancy of the total circulating red cell volume; (3) the fidelity with which the total plasma volume changes are reflected by a changing plasma cell ratio in the large vessels. The magnitude of the errors introduced by each of these factors has not been evaluated. In a series of burns, seen at the Pennsylvania Hospital, the calculated protein deficit appeared to be within 20 per cent of the quantity used in restoring the circulation to the assumed normal. This is sufficiently accurate for clinical purposes.

Discussion.—A sharp distinction should be made between plasma protein deficit and plasma dosage in severe burns. The magnitude of the protein deficit is only one factor in determining the plasma dosage. Other factors which must be considered are (1) blood volume depletion apart from plasma protein loss; (2) location and depth of burn, as well as area involved; (3) time elapsed after burn; (4) rate of protein leakage from vascular bed; and (5) complicating factors, such as condition of the heart and kidneys, degree of generalized edema and auxiliary medication (cortical hormone). The state of the peripheral circulation is the final criterion for giving plasma transfusions during the first two or three days following the burn. If, on taking all factors into consideration, a given dose of plasma does not produce the expected change in peripheral circulation, additional plasma must be given.

At no time during the course of a burn is it advisable to compensate completely for the plasma protein loss by a single large transfusion, given rapidly. For the first 40 hours plasma continues to leak from the capillaries, and if a large transfusion be given within that time, an appreciable amount of the transfused plasma leaks out.¹ It is the authors' policy to give, during this period, continuous plasma infusion in sufficient quantity to (1) keep the patient out of circulatory failure; and (2) keep the hematocrit down to within 10 points of normal for that particular patient. After the period of excessive plasma leakage the hematocrit and plasma protein are again determined, and the deficit calculated. Then plasma, equivalent to 80 or 100 per cent of the calculated deficit of protein, is given slowly by a continuous drip. A quantity of plasma greater than the calculated deficit would increase the blood volume above the normal. Too rapid an infusion might lead to cardiac embarrassment or to pulmonary edema in a patient with poor reserve. As pointed

out by Harrison and Picken,¹⁰ the last two complications are very real dangers when giving an overdose of plasma.

The present tendency for standardizing plasma dosage according to arbitrary rules is mentioned to deplore the practice. It would seem better to fit the plasma dose to the patient rather than to fit the patient to the rule. An arbitrary dose of plasma may be insufficient to correct the circulatory impairment in one patient. The same quantity of plasma may be a huge overdose, which will produce dire consequences in another patient.

CONCLUSION

A simple chart showing the relationship of plasma loss and hemoconcentration in severe burns has been constructed from the authors' equation. The plasma protein deficit in burned patients may be read from this chart when the hematocrit, plasma protein level and body weight are known. Under certain conditions accurately determined hemoglobin levels may be substituted for the hematocrit value.

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RECENT TRENDS IN THE THERAPY OF BURNS*

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AND

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FATAL BURNS cause death mainly in three ways. Deaths within the first 48 hours are usually due to shock. Those from the fourth to the seventh day are usually due to changes in the parenchymatous organs and the late deaths are usually due to infection and malnutrition.

The *systemic* treatment of burns has been developed on the basis of the experimental work of such men as Underhill, Blalock, and Harkins, and now appears to provide a sound basis for the treatment of shock. It has not, however, made such convincing progress in the prevention of damage to the parenchymatous viscera. The result, therefore, of improved systemic treatment has been to prevent some deaths but merely to postpone others.

The problem of infection is no longer solely in the domain of local treatment. The sulfonamides have come to occupy an important place in the treatment of burns as they have in the treatment of all other types of open wounds. They are useful systemically as well as locally. Since the advent of the sulfonamides, the local treatment of burns, which was stabilized in 1925 by the advent of tanning, is now in a state of flux. The closed methods represented by applications of tannic acid, silver nitrate, gentian violet, or triple dye are challenged by a variety of open methods including vaselined gauze and compression dressings (Koch and Mason), sulfanilamide powder and vaselined gauze (Colebrook), saline compresses, and sodium hypochlorite irrigations with the aid of oiled silk envelopes (Bunyan and Stannard). Plaster encasements have been used recently with success in England. A compromise method of considerable promise is the sulfadiazine triethanolamine spray devised by Pickrell. This combines the advantages of the local application of sulfadiazine with the formation of a dry semitransparent membrane which is adherent to the burned surface, yet apparently forms without coagulating living tissue.

As shock has been the most important cause of death its treatment will be considered first. It is now generally agreed that a reduction in blood volume is the most constant change in shock and that restoration of the blood volume results in striking clinical improvement. Furthermore, in shock, due to burns, the loss of blood volume is almost entirely a loss of plasma as opposed to cells. For this reason, in burn shock, the hematocrit may be used as a measure of the plasma loss.

The most important developments in the field of shock therapy in burns are:

- (1) Recognition that the physiologic requirement of the burned patient is plasma.

* Read before the New York Surgical Society, March 11, 1942.

- (2) That plasma should be given quantitatively.
- (3) That over half the plasma loss may occur within an hour of the burn.
- (4) That there is a continued loss of plasma for some time after the burn.
- (5) That the rate of loss probably varies with the amount of plasma in the circulation as well as with the severity of the burn.

The high hematocrit and hemoglobin concentrations occurring in the blood of burned patients led Underhill to regard dehydration as an important aspect of burn pathology. Fluids were forced by mouth, if the patient was able to drink, and were given parenterally in the form of glucose and saline solutions, if vomiting occurred.

Interestingly enough, excellent evidence of the difficulty of replacing lost plasma with colloid-free solutions was obtained as early as 1920, when Smith and Mendel showed that a rabbit could be given intravenously an amount of saline equal to his entire plasma volume as rapidly as possible and that by five minutes after the infusion over 90 per cent of the fluid would have left the circulation.

More recently, Minot and Blalock have shown that the intravenous administration of colloid-free solutions to animals in shock actually augments the plasma loss, that is, it washes the plasma protein out of the circulation.

The use of whole blood transfusions was undoubtedly an advance; however, as there is little loss of erythrocytes and as the blood of burned patients is already too concentrated, it is illogical to use whole blood if plasma is available. This is particularly true if the plasma is still leaking from the circulation. It should be remembered that the viscosity of the blood increases much more rapidly than the hematocrit, as blood becomes more concentrated. Trusler, Egbert, and Williams have recorded failure to relieve the blood concentration of a severely burned patient by means of whole blood transfusions. Only after resorting to plasma transfusions were they able to bring about clinical improvement in this case.

The special usefulness of plasma in the treatment of burns is now widely accepted. There is, however, much less appreciation of the quantity of plasma commonly lost by patients with burns. There is rather good evidence that the loss of plasma usually amounts to at least 30 per cent before very marked clinical symptoms appear and that in burns of moderate severity it may frequently amount to as much as 40 to 50 per cent. As the total plasma volume of a 154-pound individual is normally 3,500 cc., the loss commonly runs from 1,200 to 1,700 cc. A 500 cc. infusion will, therefore, be a step in the right direction but will fall far short of the full requirement of the patient.

An important observation which has been made by various authors is that a marked reduction of the plasma protein concentration commonly develops simultaneously with the rise in the hematocrit so that within an hour or two

after a burn hypoproteinemia appears. This, of course, calls for additional amounts of plasma.

It should be emphasized that it has been the development of the blood bank and the availability of large amounts of pooled plasma which have made quantitative treatment of burn shock with plasma practical.

The plasma loss begins almost at once and a 20 per cent loss has been observed within 15 minutes after a burn in a case treated at the Pennsylvania Hospital. It is essential to have plasma available for immediate infusion in cases of this type. Another important point in the management of burn shock is the question of the duration of the plasma leakage. Investigators do not

*Relation of Plasma Transfusions to
Loss of Plasma Protein from the Circulation.*

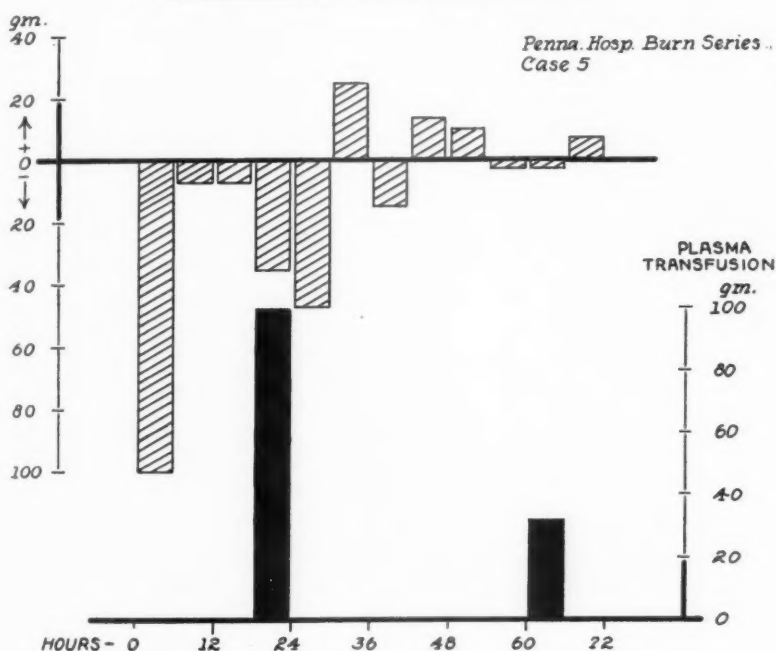


FIG. 1.

agree on whether this leakage is both local and general, or whether it is purely local, but there is no question that it persists for some time after the burn. The work of Elkinton, Wolff, and Lee gives the plasma volume curves of four patients, and indicates the response of burned patients to large plasma infusions at varying periods after the burn. The infusions given after the fortieth hour were for the most part retained, whereas those given before the fortieth hour were largely lost. Undoubtedly there is some individual variation, but these studies gave the first real indication of the duration of the increased capillary permeability. Furthermore, they indicate another point of some importance, and that is that the addition of large amounts of plasma to what may be termed a leaky circulation leads to a more rapid plasma loss, with the

result that a greater total quantity of plasma is extravasated than would otherwise have been the case. Blood chemical studies on these patients were done at six-hour intervals so that it is possible to estimate the relative amounts of plasma protein in the circulation at the end of each six-hour period and by knowing how much plasma the patient received during the period, it is possible to calculate how many grams of protein were lost each six hours. Figures 1 and 2 show the result of such a study. In the first, a large infusion was followed by a large increase in the plasma loss. In the second, as long as the plasma was given in small quantities, relatively little loss occurred (Case 9). Therefore, until a satisfactory method is found for restoring capillary permeability to normal promptly, it seems better to administer the plasma

*Relation of Plasma Transfusion to
Loss of Plasma Protein from the Circulation.*

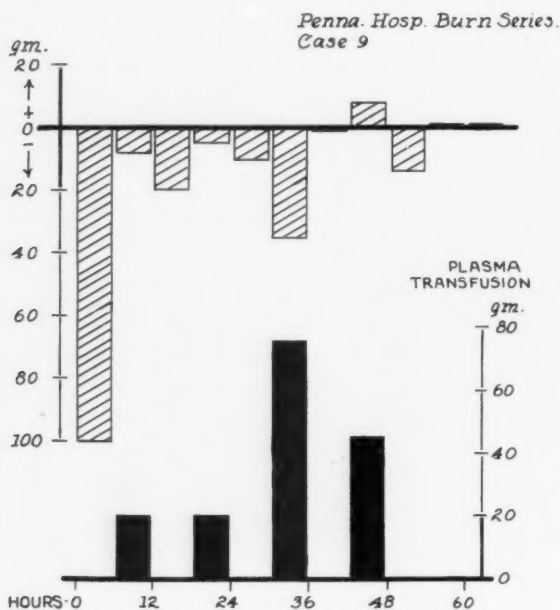


FIG. 2.

gradually by continuous intravenous drip, rather than to give large infusions rapidly before the capillary permeability has had time to recover.

Several other measures have been recommended for treatment of burn shock. Morphine remains generally accepted. The head-down position is often of value as a temporary measure. The use of oxygen has been endorsed by Schnedorf and Orr, and its usefulness in severe shock questioned by H. A. Davis. As the anoxia of burns is a stagnant anoxia and not due to any lack of oxygen in the alveoli, it is unlikely that oxygen will be of very dramatic value in burn shock, though it must add something to the saturation of the arterial blood. The value of external heat has been investigated, and experi-

mental evidence by Blalock and Mason, shows that excessive external heat hastens the deterioration of animals in shock. It is thought that this is due to the opening up of peripheral vessels with a resultant diminution in the availability of blood for vital centers. Temperatures up to 85° F. are probably safe and clinical experience indicates that they are desirable.

In the field of *local* treatment, developments have been many and recommendations numerous. Many of the new forms of treatment are, of course, mere elaborations of earlier methods. Out of much that is controversial, two important trends are discernible: first, a distrust of the tannic acid treatment; and, second, an increasing use of sulfonamides. In both these trends the British have been leaders. Tannic acid is considered by Wakeley to have



FIG. 3.

FIG. 4.

FIGS. 3 and 4.—Picture October 23, 1941, showing distribution of burn. Sulfonamide powder is conspicuous.

given bad results in burns of hands and face. Wakeley presented roentgenograms of hands showing sterile necrosis of the distal phalanges attributed to the constricting effect of the eschar on the circulation. In facial burns instances of ectropion with corneal ulceration were also reported. While the British are not unanimous on this point, such a large majority feel that the stronger tanning agents should not be used on hands and face that they have been largely given up in this Country for these areas. It would seem that the sulfonamide preparations are among the most promising substitutes.

The use of sulfanilamide in the local treatment of infected burns was begun by Leonard Colebrook on a series of 32 men evacuated from Dunkirk. In our experience, it has been the most efficient agent for clearing up infected burns so far available.

The same method has been used many times in the treatment of fresh burns. The most extensive burn in which we have used this method is shown in Figures 3 and 4. In this case sulfathiazole was employed (Rufus Dixon).

The sulfonamides are being prepared in a number of different vehicles. Straight lanolin or vaseline bases are unsuitable because sulfonamides are not oil soluble. Jelly bases, such as tragacanth, which contain water, are satisfactory, though this material may not be available because it has come from the Far East. Emulsions of oil droplets in water are fairly satisfactory bases, such as aquaphor, while emulsions of water droplets in oil are not recommended. Pickrell has developed a new type of base during the past two years at Johns Hopkins. His preparation consists of a 3 per cent solution of sulfadiazine in an 8 per cent aqueous solution of triethanolamine. This solution is sprayed on the burn after débridement and dried. After repeated and frequent sprayings a thin transparent film forms over the burned surface which becomes dry. Excellent results have been obtained with this method. Its chief drawback is that it takes considerable time to obtain a dry film, often nearly 24 hours.

With the use of any of the sulfonamides on a large burn considerable absorption takes place. The amount of the absorption is dependent to a degree on the solubility of the drug, so that higher blood levels are apt to be obtained with sulfanilamide than with sulfathiazole. Hooker and Lam have reported levels as high as 33 mg. per cent following the local use of sulfanilamide. Nevertheless, sulfanilamide reaches much higher concentrations on the burned surface than do any of the other drugs. In these concentrations it is active against staphylococci and as it is perhaps the least dangerous of the sulfonamides, many persons regard it as the drug of choice for local application. The fact that it can be crystallized in granules, like sugar, prevents the caking which sometimes occurs with sulfathiazole powder. The sodium salts of sulfathiazole and sulfadiazine are soluble, but they are too alkaline for local application.

If Pickrell's method is used, the dry film becomes impermeable so that absorption of the drug ceases within one or two days. Sulfadiazine may be supplied to the area by way of the blood stream after this time by giving the drug orally in doses of 4 to 6 Gm. per day.

If sulfathiazole or sulfadiazine therapy is used it is most important to maintain a urine output of at least 1000 cc. If this is not achieved the drug should be stopped or at least used with great caution.

A number of men have recommended the routine use of sulfonamides by mouth after all important burns. The possibility of toxic hepatitis should be kept in the mind because liver damage occurs after most serious burns and it is conceivable that such damage would predispose to liver damage due to sulfonamides. Apparently, this does not occur with much frequency among young individuals but caution should be employed in patients who are aged, and probably in chronic alcoholics as well. Toxic hepatitis rarely if ever occurs following the administration of sulfadiazine.

RECENT BURN THERAPY

Davidson originally maintained that one of the advantages of the tannic acid method was that it stopped the local loss of plasma from the burned surface. Numerous studies have shown that the major portion of the lost plasma goes into the tissues and is evident clinically in the form of edema under and about the burn; nevertheless the bleb fluid in second-degree burns often contains 5 to 6 per cent of protein and is probably very similar to plasma. There is no question but that burns treated by open methods, such as sulfanilamide powder and vaselined gauze, continue to weep large amounts of fluid so that the dressings are often saturated each day. If ample plasma is available this may not be a serious disadvantage, but wherever a large number of burns occur together and the available plasma is limited in amount, a method that rapidly tans the weeping areas may permit the saving of more plasma and hence of more lives than the open methods.

Of the other methods of local treatment little can be said. A return to the use of the bath-tub supplemented by careful cleansing and compression dressings has given excellent results in the hands of Koch, in Chicago. Some of the British writers advocate the use of saline compresses alone. The most radical development in bath treatments is the Bunyan Stannard envelope. This is a waterproof oiled silk envelope, made in various shapes so as to loosely encase a limb or a zone of the trunk. The end, or ends, of the bag are cemented to the skin and the space between the skin and the bag filled with saline or weak sodium hypochlorite solution, and irrigated. In some instances continuous irrigations have been carried out and in others irrigations have been used at intervals and the bag inflated with air or oxygen between times. Dilute sulfonamide solutions can also be employed in this way. These envelopes have the great advantage over the old continuous tub treatment, in that they segregate the burned area from other contaminated parts of the body. The mechanical difficulties of keeping the seals waterproof are obvious.

Triple dye preparations have been used extensively both in this country and abroad. They apparently occupy an intermediate position between the stronger tanning agents, tannic acid and silver nitrate, and the sulfonamides and are considered less destructive to tissue than the former but more destructive than the latter. Triple dye does produce an eschar but it forms more slowly than with 10 per cent tannic acid or 10 per cent silver nitrate.

The effect of both local and general measures on the *toxemia* of burns is still a matter of conjecture. It is known that liver necrosis and many of the other changes may be produced merely by shock due to blood loss. Under these circumstances the necrosis is attributed to anoxia and to the fact that the liver cells are very sensitive to oxygen want. However, in a number of the patients studied at the Pennsylvania Hospital, liver function tests gave evidence of severe liver damage, even in patients who were never severely shocked clinically. All patients in which these tests were carried out gave some evidence of the impairment of liver function.

This, coupled with the observation that the changes in liver function begin about the time that the edema fluid is being reabsorbed from the burned

areas, inclines us toward the belief that the changes are due to absorption of toxic materials.

Because the liver apparently suffers so acutely in burn toxemia, treatment has been aimed mainly at preventing liver damage and providing supportive treatment designed to facilitate liver repair. It is obviously important to prevent stagnant anoxia and to give sufficient plasma to maintain the circulation clinically from the earliest possible moment. Glucose should be given parenterally until the patient can retain food, when a high carbohydrate, high protein diet (Ravdin, Vars, and Goldschmidt) should be given in sufficient quantity to cover the basal caloric requirement with a 50 per cent excess. Reasons have been advanced for the administration of vitamin C and of thiamin chloride and a liberal vitamin intake should be assured. The early claim that tanning fixed the toxic materials in the tissues has neither been proved nor disproved. The counter claims that the liver necrosis was due to the absorption of tannic acid has not been confirmed.

The most important new factors in the *late* treatment of burns are undoubtedly the Padgett dermatome and the sulfonamides. Small quantities of sulfanilamide crystals do not prevent grafts from taking and do minimize infection during the interval prior to the first dressing. A burned patient is never really safe from bacterial invasion until epithelization is complete and scar tissue continues to form in granulating areas until an epithelial covering is obtained. With the calibrated thickness graft and a field prepared early with the use of sulfonamides, epithelization can be accomplished earlier and the end results are much less disfiguring than has been the case with pinch grafts.

CONCLUSIONS

In conclusion, we may list the more important recent advances in the treatment of burns:

- (1) The selection of plasma transfusions for treatment of burn shock.
- (2) A realization of the extent, the rapidity of onset, and the duration of the plasma loss and of the advantage of gradual but quantitative replacement.
- (3) The use of sulfonamides in the prevention of infection, especially of sulfanilamide for local application and of sulfadiazine for oral administration.
- (4) The development of the dermatome for covering the third-degree areas soon after granulations become visible.
- (5) Recognition of the importance of nutrition in maintaining the patient with extensive third-degree burns.

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DUTIES OF A SURGEON

"Chirurgion, looke to the wounded; and winde up the slaine. with each a bullet or weight at their heads and feet to make them sinke: and give them three gunnes for their funeral. Swabber, make cleane the ship. Purser, record their names. Gunners, sponge your ordnance. Soldiers, scour your pieces. Carpenters, about your leakes. Boatswaine and the rest, repaire sails and shrouds; and, cooke, see you observe the morning watch. Boy, fetch my cellar of bottles. Master, lay him inboard, loufe for loufe. Midshipmen, see the tops and yards well manned with stones, fire pots, and brass bales."

—Capt. John Smith, "Seamen's Grammar". (1652).

THE LOCAL TREATMENT OF THERMAL BURNS*

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THE LOCAL TREATMENT of thermal burns is of great importance during wartime. Its correct application depends, however, as much on the correct observation of certain general principles of burn management as on the choice and use of some particular remedy. Local treatment is most effective when scientifically applied.

One of the most important of the principles guiding the use of local therapy is the principle of correlation with general treatment. Pack and Davis (1930) stated in this regard that in burns it is "penny-wise and pound-foolish to consume invaluable time in applying perfect local dressings, while the patient is sinking into irrecoverable shock." The obvious advantage of coordinating the local and general treatments does not imply, however, that all local therapy should be postponed until general measures have been completed. Several years ago patients were treated locally with scant regard for general remedies; now the pendulum has in many instances swung too far the other way. While it may not be wise to radically débride a severely burned patient until shock is controlled, a few early and intelligent applications to the burned surface may not only prevent later infection, but actually diminish the progress of shock and associated fluid loss.

The general treatment of burns (Lam, 1941) includes the control of shock, toxemia and sepsis. The general treatment of burn shock, in turn, involves the use of empiric and symptomatic remedies such as morphine, warmth, and vasospastic drugs, as well as (and probably much more important) the use of plasma (or whole blood), oxygen, and possibly adrenal cortical extract. The control and restoration of fluid loss is undoubtedly the cornerstone of all shock treatment. It is only recently that the work of Lee and his collaborators (Elkinton, Wolff and Rhoads) has put the treatment of burn shock on a quantitative basis. This work of the Pennsylvania Hospital group has established the general treatment of burns as a relatively exact science, just as Davidson (1925) improved the local management.

Aside from the all-important principle of correlation with general treatment, several other rules should guide the local therapy of burns. These include: (1) Principle of regional variation. (2) Principle of time. (3) Principle of closure of the wound.

The principle of regional variation implies that not all portions of the body when burned respond in the same manner to the application of medicaments. A specific example of this is the current wave of prejudice against tanning the face and hands. This feeling is especially prevalent in Great Britain and is even had by those who favor tanning other regions of the body. It is quite probable that tanning is not the best method of local treatment for burns of the face, hands, genitalia, perineum and flexor creases of the body.

* Read before the New York Surgical Society, March 11, 1942.

The principle of time implies that what may be an adequate treatment six hours after a burn is not suitable 60 hours following the injury. Contrariwise, the fact that certain treatments are suitable for old burns (*e.g.*, continuous saline baths) does not imply that they are ideal for acute cases in which shock may be present. This same principle works in other branches of surgery, *e.g.*, the time limit of closure of a compound fracture or the removal of a ruptured appendix, and is likewise modified by other factors than time alone. Since tannic acid seals over thermal wounds, it seems logical that much the same restrictions on its use should be adopted as for primary suture of traumatic wounds. The general appearance of the burn is an influencing factor as well as the time after the injury, but it would be a good arbitrary rule to adopt never to apply tannic acid without some good reason after the first 24 hours. It is certainly true that in certain cases tannic acid may be used on old granulating wounds, as, for example, bedsores, but these should be selected with caution and the degree of tanning obtained is often a disappointment. In Great Britain there has recently been a discussion concerning the merits of late tanning and retanning of burns. Mitchiner (1940) stated: "If sepsis occurred the eschar should be removed at once and the area retanned." Cohen (1940) and Ross and Hulbert (1940) advised late tanning. Heggie and Heggie (1940) treated several infected burn cases by cleansing and retanning, using silver nitrate as the antiseptic. Hamilton Bailey (1938) stated that tannic acid can safely be used up to 72 hours after a burn, but Murless (1940) believed there are no time limits, and he applied tannic acid followed by weak methylene blue or brilliant green solution even on old infected burns. Murless stated that pus formation is not an indication for removal of the coagulum or even for incising it. He believed that the mechanism of the beneficial action is much like that of the Orr treatment of fractures applied by Trueta for infected wounds in Spain. Cohen (1940) and Atkins (1940) arguing from experience gained in the evacuation from Dunkirk, also permitted late tanning. These ideas may have some merit, but seem much like a reversion to the old sophistry of laudable pus.

The principle of closure of the wound will be further discussed under the head of skin grafting. It merely involves the prompt grafting of any granulating surface. An arbitrary rule might be made that grafting should be done whenever a granulating surface resulting from a burn is more than 5 cm. in diameter or looks as though it would take more than three additional weeks to heal. Exceptions to this rule should be few. The mistake of grafting too little or too late is far more frequent than the reverse. No conscientious surgeon would think of doing a cholecystectomy if he did not know how to close the abdomen, but many physicians attempt the care of third-degree burns who do not know either how or when to graft. The responsibility of the man who first takes care of a deep burn does not end until the surface is epithelized; that is, until the principle of closure of the wound has been observed.

METHODS OF LOCAL TREATMENT

The local treatment of burns is at present in a state of flux. Those who have felt secure in the use of tanning or other standard therapies are beginning

to feel the impress of the newer sulfonamide methods. Recent international developments have increased both the importance of burns and the necessity for a prompt, even if not final, standardization of treatments for use during the period of emergency. In a recent publication (1942) the author discussed over a hundred local treatments of burns. Local treatment has also been reviewed by Penberthy and Weller (1939), Harkins (1936-1938), and McClure and Harkins (1942). In the present discussion, several of the more important or novel groups of these treatments will be discussed. It is only by a survey of the present methods at hand that guidance in the choice of future therapy can be had. Furthermore, as brought out in the discussion of the principles of regional variation and of time, it is of advantage for the surgeon to have more than one method of local treatment at his disposal to fit the peculiarities of the particular case at hand.

(1) *Tanning agents*.—These include tannic acid itself in the form of a spray, jelly, powder, or both; tannic acid-silver nitrate; cutch extract; tea; ink; ferric chloride (Coan, 1935); picric acid; aluminum acetate; acetic acid; and several others. Some of the last named in this list are more properly defined as styptics or astringents than as actual tanning agents. Most of the others are variants of tannic acid alone or in compound form. Tannic acid is a readily soluble, nonnitrogenous, amorphous powder obtained from Aleppo galls. It is only slightly antiseptic and is readily contaminated in solution, but in powder form lasts indefinitely when kept protected from light and moisture. On application to a burn surface it forms a white precipitate with the proteins of the exudation from the weeping epithelium. Tannic acid was used by Davidson (1925) as a means of controlling toxin absorption, but whether this or prevention of fluid loss is its chief action is as yet undecided.

Tannic acid may be combined with various antiseptics such as

- (1) Mercuric chloride, 1-2,000 (Mitchiner, 1938)
- (2) Acriflavine, 1-1,000 (Wilson, 1934)
- (3) Merthiolate, 1-5,000 (Noland, 1935); 1-10,000 (Martin, 1938)
- (4) Dettol, 1-5 (Clark and Cruikshank, 1935)
- (5) Salicylic acid, 1-1,000 (Fantus and Dyniewicz, 1937)
- (6) Hexyl-chloro-m-cresol, 1-1,000 (Hartman and McClure, 1938)
- (7) Sulfonamide drugs

The use of sulfonamide drugs in combination with tannic acid has considerable promise.

Tanning agents have the advantage of rapid action with minimum subsequent nursing care. Usually a 5 per cent solution is advised, but for war use a more rapid tanning is helpful and for this purpose either a more concentrated solution (20 per cent) or combination with silver nitrate (Bettman method, 1935) is suggested. Since the accouterments of the spray technic are best restricted to hospital use, application of a water soluble tannic acid jelly is an advisable first aid remedy. The use of such a jelly will not interfere with subsequent tanning in the hospital and in addition despite its slowness will often have effected an adequate eschar by the time the hospital is reached, obviating the need for subsequent additional tanning.

The importance of repeated painting of the edges of the tanned eschar with various antiseptics has been emphasized in reports of war surgery coming from

Great Britain. Butler (1940) advised a water soluble tannic acid jelly, then an 85° to 100° F. tannic acid bath for 30 minutes, after which 10 per cent silver nitrate is applied. A heat cradle kept at 85° to 90° F. is then put over the patient and the margins are painted three times daily with 1 per cent gentian violet solution. Wallace (1940) painted the edges of his burns daily with gentian violet or acriflavine. Heggie and Heggie (1940) cleansed and retanned several infected cases with good results, especially when the margins were repeatedly painted with antiseptic dyes. In the treatment of war burns Cohen (1940) used 5 per cent tannic acid followed by 10 per cent silver nitrate to produce rapid tanning. For face burns he applied a little petroleum jelly to the eyelids and held cotton wool over them during application to protect the eyes. He reported that burned areas are usually infected from the adjacent skin and that the streptococcus is the commonest type of invader. Brilliant green was found to be particularly effective in preventing such infections, and in his series, he painted the edges of the tan daily with 1 per cent brilliant green in 30 per cent alcohol. This was of special importance for burns of the scalp, forehead and neck. By careful attention to this regimen he was able to keep the scabs on these regions absolutely dry in all cases but two. In his series of 70 cases, 37 were treated by the silver nitrate-tannic acid method with no deaths. The other 33 were treated by either methyl violet or tannic acid before admission, with two deaths, one soon after entrance and one four days later.

The previous application of greasy or oily preparations markedly interferes with subsequent tanning treatment. Benzene, ether, soap, and ether soap (Fantus, 1934) are useful cleansing agents. In wartime, however, most of the burns which are contaminated with grease are received in naval actions and inflammable detergents are not desirable on board ship. To get around this difficulty, the British have used a compound known as red turkey oil.

(2) *Dyes*.—The frequent occurrence of streptococci in burns after the first 12 to 24 hours is well known and has been substantiated by the researches of Aldrich (1933) and Clark and Cruickshank (1935). Moorhead went so far as to define a burn as "an infected wound caused by heat." Aldrich introduced the gentian violet treatment in 1933 at the suggestion of Firor to combat this streptococcal infection. The use of gentian violet alone or in combination with acriflavine and brilliant green in the form of the so-called triple or compound dye presents the advantages of antiseptic action and lack of possible destruction of skin islands. On the other hand, its slow action and staining properties render it less useful for combat purposes. However, in combination with silver nitrate it presents practically the same merits as the combination of tannic and silver nitrate.

The triple dye of Aldrich (1937) has the following prescription:

	Gm. vel cc.
R Crystal violet.....	45 00
Neutral acriflavine.....	22 50
Brilliant green.....	30 00
Water, to make.....	3000 00

(3) *Sulfadiazine spray*.—As advocated by Pickrell (1941) this is given every hour the first day, every two hours the second day, every three hours the

third day, and every four hours the fourth day. This complicated regimen alone argues against wartime use of the method. In addition, the resultant eschar is so thin that second-degree burns are apt to be painful and transportability of all types is interfered with. This may be the treatment of the future, but at present is not established well enough for general adoption.

(4) *Ointments*.—These include those containing sulfanilamide, sulfathiazole, sulfadiazine, or cod liver oil. The author has had most experience with sulfathiazole and cod liver oil, although sulfadiazine may be better. The chief use of these ointments would seem to be on the face, hands, feet, and genitalia. On the extremities, they may be used in the form of pressure dressings.

(5) *Oiled silk (Bunyan) envelopes*.—These are chiefly useful in the later stages of burn treatment, although in deep burns of the hands they may be applicable early. The envelopes combine the advantages of the bath method popularized by the Vienna school of dermatologists, Rose of Seattle (1936, 1937), and by Blair and Brown and their associates (1931–1938), as well as of the warm moist air treatment of Smith, Risk and Beck (1939). While the original method described by Bunyan (1941), and used by Hudson (1941) and Hannay (1941), requires irrigation with a special electrolytic solution of sodium hypochlorite, this is not essential and the principle of the envelope is the same when saline or Dakin's solutions are used. It is important that the temperature of the solution be as close as possible to 100° F. Various shaped envelopes can be made to fit different parts of the body requiring treatment. Bunyan reported favorably on use of the method in 200 cases of burns and wounds while Hudson (1941) reported on 27 cases of burns alone. Wakeley (1941) lists the following advantages of the Bunyan envelope method in the treatment of war burns:

- (1) It can be easily and quickly applied.
- (2) The treatment is painless, there are no dressings, and the patients do not lose confidence or become depressed.
- (3) Rapid epithelization takes place and can be seen through the envelope. Skin grafting can be performed at any time after irrigation with saline solution instead of hypochlorites.
- (4) The envelope allows of free movement of the limb without the fear of pain.
- (5) In the difficult cases where fractures exist as well as burns, this method appears to offer a solution. Treatment of ordinary compound fractures has proved successful.

THE IMPORTANCE OF EARLY SKIN GRAFTING

Third-degree burns are by definition those which produce granulating surfaces. As already stated under the discussion of the principle of closure of the wound, early grafting is one of the most neglected fields in burn treatment. A psychologic anxiety should be bred in all surgeons over every extra day that such a wound remains unepithelized. Keloid, contractures, malignancy and increased unsightliness are all more liable to occur with delayed healing.

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General care of the patient with control of anemia and hypoproteinemia are essential. Efforts should be made to hasten spontaneous healing, but as Brush and Lam (1942) recently reported, the application of external stimulants of epithelial proliferation are of more psychic than material benefit. Saline soaks and dressings, cod liver oil, acriflavine, oxyquinoline sulphate scarlet R gauze (Bettman, 1931), and sulfonamide drugs all have their place in this phase of the treatment.

Skin grafting itself should depend on small deep (pinch) grafts, thick split (Thiersch) grafts, and dermatome grafts. Of these, the third type is used almost to the exclusion of the other two in the author's practice and will be described more in detail below. Full-thickness and pedical grafts have no place in the early plastic care of burns and should be reserved for subsequent corrective and restorative late plastic care. This latter is done when epithelization is complete.

The technic of taking and applying dermatome grafts can be divided into 12 steps which embody principles laid down by Blair, Brown, Davis, Padgett, Harkins, and their associates, as follows:

(1) *Preoperative Preparation of Granulating Area.*—The best immediate preparation is to apply saline dressings for at least 24 hours just before operation. Decision as to the time for grafting depends more on the presence of (a) a healthy pink appearance of granulations, (b) lack of anemia, and (c) lack of hypoproteinemia, than on any bacterial counts or other indirect observations.

(2) *Preparation of Donor Site.*—The skin is cleansed with ether followed by alcohol and painted with the special adhesive glue which is allowed to dry for about 60 seconds before taking the graft. The use of ether is important as the glue will not adhere to a greasy surface.

(3) *Anesthesia.*—Because of the large surfaces involved and because the grafts are usually sutured in place, gas anesthesia is generally adopted.

(4) *Removal of Grafts.*—If the granulating area is the size of the drum surface, one drum of skin is taken. If the desired graft is to be smaller, only part of the drum is coated with the special adhesive glue. If a much larger area is to be covered, several drumfuls of skin are taken and are either applied individually, or better, sutured together in the pattern of the defect to be grafted after the manner of a patch-work quilt according to the method of McPheeters and Nelson (1941). In any case, the adhesive glue is best applied to the drum in a thick layer at one end and smoothed over the drum in as thin a layer as possible using the base of the dermatome stand to distribute the glue. The drum (with the knife set at about 0.6 Mm. thickness (less for children or those with atrophic skins) is held in the left hand and the knife in the right. Two practical points are to press the upper end of the drum very firmly against the skin where the cutting is to begin, as a good start is essential, and not to allow any assistants to retract the skin as this merely pulls it away from the drum and is harmful. Gradually turning the drum with the left hand and cutting backward and forward with the right, a

graft the size of the drum surface and of uniform thickness is quickly obtained in a majority of the cases.

(5) *Dressing Donor Site.*—Five grams of sulfanilamide powder are sprinkled evenly over each area 4 x 7 inches (equal to one drum surface) and this is covered with sterile fine-mesh vaselined gauze followed by dry gauze and a tight adhesive tape dressing.



FIG. 1.—Example of neglected burn. This boy was burned 27 months before this picture was taken and he was never grafted during all of this time. This neglect of the principle of closure of the wound has resulted in a severe condition, including bony ankylosis of the right elbow and left temporomandibular joints, ectropion of the right eye with tearing, and a web deformity of the neck not shown in this picture. Subsequent plastic care improved this patient markedly, but not so much as it would have, if applied earlier. (From Harkins, H. N.: *The Treatment of Burns*, Springfield, Ill., Charles C. Thomas, 1942.)

(6) *Transfer of Grafts.*—This should be done aseptically when more than one graft is to be taken. During the transfer, the graft should be kept moist with warm (not hot) normal saline solution.

(7) *Preparation of the Granulating Surface.*—Granulations are seldom shaved off a burn granulating surface that is less than three months old. Since the ideal of treatment is never to let such a surface go as long as three months, it might be said that to have to shave off granulations means previous neglect. The skin around the surface may be covered with any antiseptic, but the

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granulations themselves should be gently cleansed with ether alone. If they are at all infected, sulfanilamide powder (not sulfathiazole, as it tends to act as a foreign body) may be dusted very evenly over the granulating surface. This should be done in a dosage of 1 Gm. per ten square inches and it is essential that the coating be more homogeneous than that over the donor site. The grafts are then applied epidermal surface upwards on the sulfanilamide layer, or if this drug was not deemed necessary, directly on the granulations themselves.



FIG. 2.—Example of neglected burn. This girl, age 18, was burned 14 years previously at the age of four. She was never grafted and ulcers of the upper right thigh are still present.

(8) *Suturing of Grafts.*—All dermatome grafts should be sutured in place with fine non-absorbable material. A circumferential ring of continuous suture interspersed with several double-locks or interrupted stitches is advisable for the periphery of the graft. The edge should just overlap the surrounding live skin, while an excess of graft merely dies and invites infection. The graft should be applied with the tension and size as near as possible like that which it had before being removed from the donor area. The bed of the

graft may be sutured through the granulations to the fascia beneath with numerous interrupted stitches or criss-crossing continuous ones. These latter are especially useful when the graft covers a convex surface, as the thread between the stitches holds the graft in place. If enough sutures are placed, very few fenestrations need be made in the graft, as the needle holes permit escape of blood or exudation.

(9) *Dressing Grafted Area.*—The importance of this step is shown by the following quotation from Brown, Blair, and Byars (1935): "The dressing fixation is considered a part of the operation and upward of 30 minutes may be required to apply it correctly in extensive cases." The use of a wet dressing is useful in infected cases. In any instance the graft is covered with fine mesh vaselined or xeroform gauze (a little sulfanilamide may be sprinkled on first) and this is covered with a generous layer of cotton mechanic's waste. (Mechanic's waste is easier to handle and cheaper than sea sponges, costing only 12 cents a pound). The waste should be autoclaved before use, and gives a very uniform pressure. The dressing should next be anchored with elastic adhesive to the surrounding skin and if possible a splint or encasement applied. Too much pressure is almost worse than too little and should be avoided, but adequate immobilization should be maintained for several days. The fate of a skin graft is sealed during the first 48 hours. In cases with marked infection at the time of grafting an optional method is to incorporate perforated Dakin's tubes in the dressing. Twice daily irrigations with two quarts of saline solution (or tap-water) followed by the instillation of two ounces of sulfadiazine solution seem to be effective in controlling infection. External irrigation by constant drip as described by Harkins (1942) accomplishes the same purpose.

(10) *Changing the Dressing of the Donor Site.*—If no infection, as determined by odor, or hemorrhage results, the dressing should ideally be left intact until the area is healed. In many cases, however, the outer dressing should be exchanged for a dry fresh one during the first day or so, but the vaselined gauze should not be removed as long as it adheres (usually 12 to 14 days).

(11) *Changing the Dressing of the Recipient Site.*—This should be done at any time from three to eight days following the operation, depending on the amount of infection that is present. When the change is decided upon, it is best to soak the area for some hours beforehand so as to prevent sticking and pulling off of the grafts. Since the donor site must be kept dry, complete tub immersion is not feasible and some type of irrigation or drip is advised. Thus, if the dressing is to be changed in the afternoon, the nurse is instructed to start the drip in the morning. When the time comes for the change, the danger of pulling the grafts off with the dressing is minimal. Irrigation through Dakin's tubes incorporated in the dressing accomplishes the same thing. The stitches may be removed in part at the first dressing although any adherent sutures should be left until at least the seventh postoperative day. Subsequent dressings do not need pressure but can utilize vaselined gauze, sulfanilamide powder, and moist gauze or irrigations with advantage.

(12) *After-Care.*—Once the dressing of the recipient site has been changed,

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renewals at about 48-hour intervals are necessary until the skin has become firmly established, at which time the bandage may be removed entirely.

When the surface is epithelized and the principle of closure of the wound has been fulfilled—then and only then—the responsibility of the surgeon originally caring for the burn ends.

COMMENT

For wartime use, simplicity and rapidity of action are essentials of burn treatment. The ideal treatment would probably be the best under all circumstances, but at present it is possible that the methods of burn treatment most suitable in the leisurely course of peacetime practice are not necessarily best fitted to the urgency of war. A rapid tanning of the broad surfaces of the body seems best fitted to the latter.

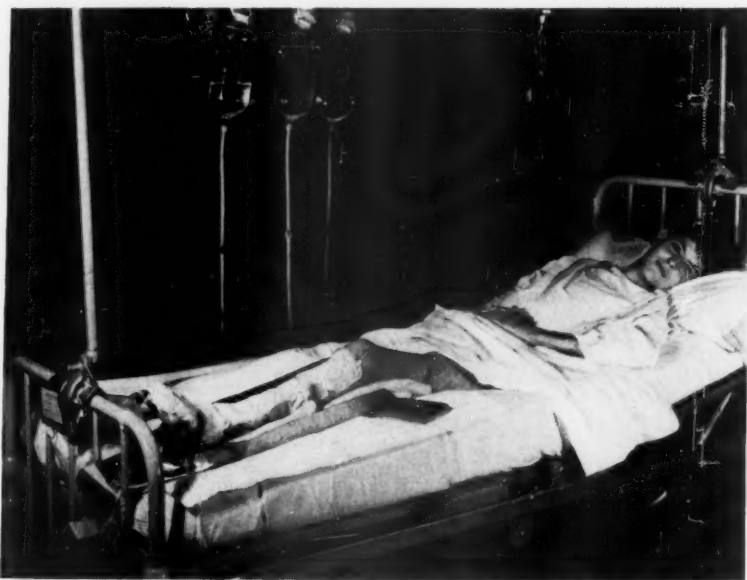


FIG. 3.—Simple type of external drip used in local care of burn or skin grafts. (From Harkins, H. N.: *The Treatment of Burns*, Springfield, Ill., Charles C. Thomas, 1942.)

Since it is extremely difficult to determine the exact depth of injury until late in the course of a burn, even when viewed by experts under the best of conditions, there is little use in recommending wartime determination of burn depth in deciding upon burn treatment. On the other hand, the site of the burn is of considerable significance in this regard. Tanning methods seem less well suited to the face, hands, feet and perineum than do certain of the ointments.

Several problems and details of technic arise which are listed below without comment:

- (1) What is the longest possible interval after a burn that tanning therapy can be applied under optimum conditions?
- (2) What percentage of plasma loss does tanning prevent?
- (3) Assuming that the main purpose of the tanning method is to conserve plasma, if plenty of plasma is available, is tanning still advisable?
- (4) Is tannic acid toxic?

SUMMARY

- (1) Local treatment should be carefully correlated with general treatment.
- (2) Rapid tanning of the large flat surfaces of the trunk or proximal extremities seems the best local treatment for wartime use. Preliminary first aid use of the slower acting tannic acid jelly may be time-saving in the long run when hospital facilities are not available.
- (3) Individualization of burn therapy according to the site of injury is of importance. The face, hands, feet and genitalia should be given separate treatment, such as sulfathiazole or sulfadiazine ointment.
- (4) Early skin grafting is of prime importance in all third-degree burns.

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THE PROCUREMENT AND USE OF BLOOD SUBSTITUTES IN THE ARMY*

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THE RESEARCHES that have been conducted to find an effective means of replacing depleted circulating blood volume in traumatic shock have provided one of the most intriguing chapters in modern medicine. The developments in the field of transfusion therapy in recent years have had a marked influence on the practice of civilian and military surgery.

The contributions of Crile,¹ Robertson,² Cannon,³ and Keith⁴ preceding and during World War I firmly established the use of the blood transfusion as a safe and effective measure. The continued use of whole blood transfusions in civilian hospitals and fixed medical installations in the Army is assured. However, the limitations of whole blood and the difficulty of obtaining it immediately when needed have stimulated a persistent search for other fluids which might be equally as effective and more readily available than blood in the treatment of surgical emergencies. The desire to provide an adequate blood substitute is reflected in the researches on gelatin and acacia carried out by Hogan,⁵ and Bayliss,⁶ respectively, during World War I.

The realization of the need for effective replacement fluids other than whole blood was revived in 1936 by Elliott⁷ when he proposed the use of untyped plasma for the treatment of obstetrical and surgical shock. Renewed impetus was given to this subject with the beginning in 1938 of hostilities in Europe. This unprovoked conquest forcefully brought to the attention of our Army and Navy the necessity of preparing for any eventuality.

In May, 1940, the National Research Council was asked by the Surgeons General of the Army and Navy to act in an advisory capacity on the many medical problems that might arise in the eventuality of active conflict. As a result of this request, a Committee on Blood Transfusions and a Subcommittee on Blood Substitutes were appointed to study the problems confronting the armed services in selecting and procuring adequate quantities of suitable blood substitutes and blood derivatives.

The clinical and experimental work of Elliott,⁸ Strumia,⁹ Mahoney,¹⁰ and Levinson,¹¹ to mention only a few, fortuitously done between 1936 and 1940 strongly suggested the possibility of using blood plasma and serum, and thus paved the way for the adoption of these agents as adequate replacement fluids for the treatment of shock, burns and the emergency treatment of hemorrhage.

As a result of investigations on blood procurement, preservation and transportation of whole blood,¹² methods of preparation of dried plasma and serum,¹³ and the commercial facilities for producing plasma in large quantities, it was concluded by the Subcommittee on Blood Substitutes that dried plasma

* Read before the American Surgical Society, Cleveland, Ohio, April 6-8, 1942.

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was the blood derivative of choice for the Armed Services. Dried plasma was chosen because of its long preservation period, stability at extremes of temperature, its effectiveness as a replacement fluid and the safety with which it can be administered. It was also agreed that freezing and maintaining this fluid in the frozen state is an adequate method of storing plasma.¹⁴ Plasma preserved in this manner can either be dried from the frozen state or thawed rapidly and injected as wet plasma.

The effectiveness of plasma as a replacement fluid for military use is directly proportional to its availability under combat conditions.¹⁵ In order to make plasma accessible to medical units in the field it is necessary to package



FIG. 1.—The standard Army-Navy package of dried human plasma.



FIG. 2.—Cans being removed from package with draw-cord.

it with needles and intravenous equipment so it can be regenerated and administered immediately wherever it is needed. A package for this purpose has been developed by representatives of the Army and Navy¹⁶ in conjunction with committees of the National Research Council and this unit is now designated as the Standard Army-Navy package of dried human plasma. The dried plasma, distilled water for reconstituting the plasma, and intravenous equipment are packed together in cans so that the set may be preserved for a period of five years.

A description of this package follows:

The completed package (Fig. 3) consists of two 400 cc. bottles, stoppered with sleeve-type rubber stoppers and an intravenous assembly in sealed metal cans, packaged in a tape-sealed, water-proofed, fiber-board box. On one end of the box is a label of the biologic laboratory processing the plasma and on the other end is a Red Cross label showing that the blood from which this plasma was made was furnished by volunteer Red Cross donors (Fig. 1). The box is easily opened by tearing the tape transversely and ripping it off. The cans fit in the box snugly so a draw cord is provided to facilitate removal of the cans (Fig. 2). Also present in the fiber board box is a questionnaire to be filled out by the operator each time a unit is used. When these forms

are filled out properly and sent in for filing, it is possible to compile valuable statistical data on the use of plasma.

Keys, spot-welded to the top of each can, are provided for opening them. The can, containing the dried plasma bottle, has packed with it intravenous and double-ended needles and a metal clamp. The plasma bottle and can are sealed under a 25-inch vacuum to keep out moisture. As an added precaution, a bag of silica-gel is placed in the can to adsorb any moisture that may be present. A cloth-tape bail attached to the bottle makes it possible to suspend the container while administering the plasma.



FIG. 3.—Contents of plasma package.

The bottle containing the distilled water, together with the airway assembly and intravenous set, is sealed in another can which is filled with nitrogen. This inert gas is added to preserve the rubber by reducing oxidation to a minimum. The intravenous equipment consists of an intravenous set and an airway assembly. The airway assembly is made of nine inches of rubber tubing with a needle attached on one end for insertion into the rubber stopper and a cotton filter on the other end. The intravenous set consists of 48 inches of rubber tubing which contains a glass cloth filter for filtering the plasma as it is administered. At one end of the tube is an intravenous needle attached to a glass observation tube and at the other a short needle which connects the set to the plasma bottle.

The instructions for the preparation and use of this material are lithographed on the can containing the dried plasma.

The plasma is made ready for use by inserting the double-ended needle, provided for this purpose, through the stopper of the bottle containing the

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distilled water (Fig. 4). The water bottle is inverted and the other end of the needle is plunged into the stopper of the dried plasma bottle; the negative pressure in this container causes the water to flow in and the plasma goes into solution in about two minutes. In order to allow air displacement in the water bottle and speed up regeneration, the needle of the airway should be inserted into the stopper of the water bottle. When the water has been transferred the double-ended needle is withdrawn from the plasma bottle. The airway and intravenous set are then connected to the plasma bottle and the plasma is ready to be administered (Fig. 5).

Based upon the recommendations of the National Research Council, a program was outlined for the collection of blood and the processing and



FIG. 4.—Plasma being constituted with distilled water.



FIG. 5.—Reconstituted plasma ready for administration.

drying of plasma. The American Red Cross was asked to furnish volunteer donors for this program; the Army acted as the purchasing agent and contracts were made with eight commercial biologic laboratories for the preparation of dried plasma.

At the present time, the American Red Cross has 18 bleeding centers operating throughout the country, supplying approximately 15,000 bleedings a week to the processing firms. It is anticipated that by July 1, 1942, 350,000 packages of dried plasma will have been delivered to the Army and Navy. As rapidly as the dried plasma packages are received at the supply depots they are placed aboard combatant ships of the Navy and are issued to units of the Army going outside the country so that they will be readily available for use. Because of the urgent need elsewhere dried plasma is not being issued to medical installations for use in the United States.

Approximately 300 reports recording the use of dried plasma in hospitals in this country and at foreign stations have been returned to the Blood Research Laboratory. Two-thirds of these units were administered for the prevention and treatment of shock while the remainder were used in hypoproteinemic states. Definite improvement was observed in all but four cases treated for shock. It is apparent from these reports that when plasma is indicated, it should be started as soon as possible. The earlier plasma is injected after injury, the smaller the amount required to overcome the blood volume loss.

No severe reactions were encountered in this group. One patient developed urticaria, which was localized, and five had chills, but no temperatures above 100°F. were recorded.

It is expected that the needs for dried plasma by the armed services will be increased by threefold during the next fiscal year and therefore the program for obtaining donors and preparing plasma is being supplemented with the help of the American Red Cross.

In addition to the national program for the collection and preparation of dried plasma for use by the armed services, the Army maintains a laboratory for the investigation and preparation of blood substitutes and blood derivatives. This Blood Research Laboratory was established in May, 1940, at the Army Medical School, and has operated continuously since that time. In this laboratory, liquid plasma is being prepared from blood collected from volunteer Red Cross donors at the combined Army-Navy Donor Center in Washington. This liquid plasma is being used at Walter Reed General Hospital and shipped unrefrigerated to outlying station hospitals. During the past few months liquid plasma prepared in this laboratory has been preserved by freezing it in a regular ice cream chest. Prior to shipping, the frozen plasma is thawed out rapidly by immersing it in a water bath at 37° C. Plasma thawed in this manner does not contain precipitated protein material. The thawed plasma can be stored at normal room temperature or shipped great distances without refrigeration. This material is arbitrarily given a four-month dating period from the time it is thawed out. Further experience is required to determine how much longer this dating period can be extended. As a result of our experience with liquid plasma, it is conceivable that a dating period of one year might be placed on the thawed wet plasma.

The plasma processing unit at the Naval Medical Center now is supplying thawed wet plasma to all of their medical installations throughout the country. The plasma unit at the Army Medical School is supplying thawed wet plasma to the Army hospitals in the Third Corps Area and is now prepared to supply the First and Second Corps Areas.

During the past 18 months, about 3,000 bottles of liquid and thawed wet plasma have been used locally in the Army and Navy Medical Centers¹⁷ and shipped to service hospitals throughout the United States. Questionnaires have been supplied with these units and approximately 1,500 have been returned for evaluation. Reactions in this group have consisted of localized

urticaria, chills and fever, and, in one case, substernal pain was produced. The reaction rate in this group is .62 per cent. No fatal reactions have occurred.

Properly prepared liquid plasma is stable in the frozen state and may be preserved indefinitely. This method of preservation provides a safe and economical method of making plasma readily available to the military forces in this country. When thawed in the manner described above plasma can be shipped safely in the liquid state unrefrigerated.

Based upon the experience gained during the past 18 months at the Army and Navy plasma centers in Washington, plans have been made by the Army to establish liquid plasma processing centers in each Corps Area to supply all stations in the area, so that every Army hospital will have access to supplies of blood plasma. Plasma made in these centers will be prepared by a standard technic. The medial officers and technicians responsible for running these units will be trained at the Army Medical School and the Army-Navy Donor Center in Washington. This program is under way now and it is expected that within the next few months frozen wet plasma will be generally available to the Army.

Although dried and wet plasma have proved their value as effective replacement fluids in shock and burns, interest in other blood derivatives is constantly increasing. One of the more recent developments, the preparation of human albumin, is worthy of consideration.

Cohn,¹⁸ at Harvard, has been successful in producing human albumin in such form that it can be injected intravenously in the human with relative impunity. Albumin makes up 65 per cent of the plasma proteins and exerts approximately 80 per cent of the osmotic effects provided by the blood plasma. It is stable in the liquid form up to temperatures of 45° C. and can be prepared in 25 per cent solution which does not precipitate or become cloudy on standing unrefrigerated for many months.

Human albumin has been accepted by the National Research Council, for the Army and the Navy, as an effective blood derivative for the treatment of shock and burns. It is realized that albumin is not a completely adequate replacement fluid when the patient is dehydrated. In cases of injury complicated by dehydration states it is essential that supplemental fluids and electrolytes be administered by mouth or intravenously when albumin is injected. A word of caution should also be said about the use of albumin in patients where concealed hemorrhage may be a complication. Twenty-five per cent albumin draws fluid into the vascular bed rapidly, thereby raising the blood pressure in a short time. Wounds that are closed while the blood pressure is low may bleed following the injection of albumin, producing massive hematmata. If these occur in the neck, pressure symptoms may result. Therefore, the wounded patient should be observed carefully after albumin is injected to prevent secondary hemorrhage. Great care must be exercised in the use of 25 per cent albumin in casualties with gunshot or stab wounds

of the chest or abdomen. Where gross hemorrhage is suspected, albumin might best be withheld until the large bleeders can be tied off.

The possibility of providing an effective replacement fluid in a small package has been of tremendous interest to the Army and Navy. Since 100 cc. of 25 per cent albumin has an osmotic pull approximately twice that supplied by the Standard Army-Navy package of dried plasma, it is worthy of consideration by the military surgeon for use aboard ship and other places where space is a problem. With this in mind a container, with an intravenous assembly, for packaging and administering albumin has been developed.

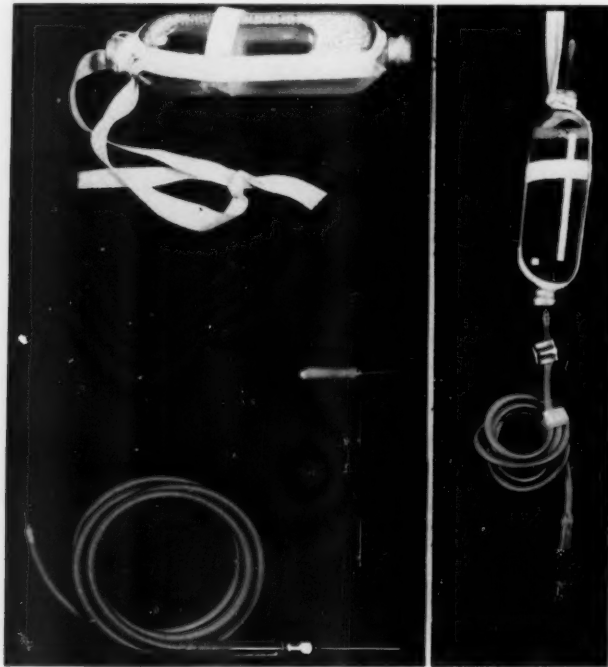


FIG. 6.—Equipment for administering human albumin.

FIG. 7.—Albumin package ready for administration.

The package (Fig. 6) consists of a 115 cc. double-ended vial closed with sleeve-type rubber stoppers. The instructions for preparing the set are baked on the glass vial. A string or cloth tape bail is provided for suspending it. The intravenous assembly consists of a small-bore rubber tube 40 inches long with a connecting needle on one end and a 20-gauge intravenous needle attached to a small glass observation tube on the other. The airway is made of a rubber tube one inch long, containing a cotton filter and a connecting needle. The albumin set may be sealed in a metal can or plastic carton under nitrogen.

The albumin is made ready for use by inserting the connecting needle of the intravenous set through the stopper at one end and the airway needle through the stopper at the other end (Fig. 7).

SUMMARY

The program for the collection and use of blood substitutes in the Army has been discussed.

A description of the methods of packaging these substitutes to make them suitable for storage and for use wherever necessary has been outlined.

The experience thus far gained by the armed services in the use of dried plasma and thawed, wet plasma have shown these methods of storage to be adequate within the limitations outlined in this paper.

It is expected that both blood plasma and human albumin will be made available for use by the Army and Navy.

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INTRAVENOUS INJECTIONS OF AMINO-ACIDS (HYDROLYZED CASEIN) IN POSTOPERATIVE PATIENTS*

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IN A paper¹ before this Association two years ago, I described clinical experiences with surgical patients who received intravenous injections of a mixture of amino-acids (Amigen†) as a means of supplying protein parenterally. Evidence of its beneficial effects, both clinical and chemical, was obtained. However, the number of cases was small and the occasional occurrence of untoward reactions seemed to demand a larger experience with this new method of intravenous protein alimentation. Accordingly, a large series of injections were made on the wards of the St. Louis City Hospital. We carried out all of the injections ourselves except that when one of us (D. O. W.) entered the Medical Corps of the United States Army, Drs. L. V. Mulligan, T. C. Tyrell, and W. H. Elliott substituted for him. All patients receiving Amigen were carefully observed and records kept on a separate form. At least one of us (E. B.) was present with the patient during all injections in order to make the observations as complete as possible.

TABLE I
SUMMARY OF INTRAVENOUS INJECTIONS OF AMIGEN

Solution Contained				Surgical (Post-op.) Cases		Medical Cases		Pyrogenic* Reactions	Deaths*
Solution No.	Amigen (Per Cent)	Glucose (Per Cent)	Prepared by	Number of Patients	Number of Injections, (Liters)	Number of Patients	Number of Injections, (Liters)		
1.....	2.5	10	M. J.	2	7	49	95	10	5
2.....	2.5	10	M. J.	8	17	5	8	1	0
3.....	2.5	10	B. H.	42	97	20	39	0	0
4.....	2.5	5	B. H.	23	39	21	26	0	2
5.....	2.5	2.5	M. J.	66	514	3	6	3	10
6.....	2.5	2.5	B. H.	55	100	15	18	1	3
7.....	5	5	M. J.	2	36	1	11	0	0
Totals..				198	810	114	203	15	20

* No pyrogenic reactions or deaths were due to Amigen (see text).

Procedure.—Preparation of Solutions: Amigen is an impalpable, nearly white powder which in water forms a clear, amber-colored solution with a pH

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† The amino-acids used were a mixture (containing also some polypeptides) made by the enzymic hydrolysis of purified casein and prepared and supplied by Mead-Johnson and Company; it is called, and will be referred to as "Amigen."

of 4.5. Various solutions were used in the present study. Their composition is listed in Table I. In general, two methods were used for sterilization. The solutions prepared in Barnes Hospital (B. H.) were passed through a single Berkefeld filter, autoclaved at five pounds pressure for 30 minutes and used soon thereafter. The solutions made by Mead-Johnson and Company (M. J.) were subjected to careful Seitz filtration, but not autoclaved; their sterility was carefully tested before use.

As is well known, many febrile reactions with chills are due to the use of distilled water containing pyrogens. These pyrogens are products of bacterial growth which may occur even in distilled water which is allowed to stand for any length of time either in a container or in some undrained portion of the apparatus which is not sterile. Freshly distilled water coming directly from the condenser of properly designed stills, is not pyrogenic; such water was employed in the preparation of all solutions used in the present study, with one exception. The first batch used (Solution No. 1) was inadvertently made up with distilled water which was later found to be pyrogenic. It is notable that ten of the total of 15 reactions, indeed all which could be explained in no other way, occurred with this solution. This defect was, of course, immediately corrected; subsequent solutions were not only made with freshly distilled water, but tested for pyrogens by injection into rabbits.

Selection of Cases.—No attempt was made to select special cases in this study except that most of them were surgical patients. The medical and surgical diagnoses are listed in Table II. Nearly all of the patients were dehydrated and ill and needed parenteral fluids; many of them were in a critical

TABLE II
DISTRIBUTION OF CASES

	Number of Patients	Number of Injections
Surgical (postoperative):		
Acute appendicitis, mostly with peritonitis.....	52	201
Intestinal obstruction, mostly due to cancer.....	15	119
Perforated peptic ulcer, many with severe peritonitis.....	12	102
Gastrectomy, mostly for cancer.....	7	85
Exploratory celiotomy, mostly for cancer.....	12	57
Herniotomy, mostly ventral.....	19	67
Fractures.....	39	65
Cholecystectomy.....	9	53
Burns.....	4	10
Miscellaneous.....	29	51
Totals.....	198	810
Medical:		
Pulmonary tuberculosis.....	43	56
Senility.....	24	36
Cardiac disease and hypertension.....	12	41
Pneumonia.....	10	19
Alcoholism.....	3	4
Arthritis.....	7	12
Miscellaneous.....	15	35
Totals.....	114	203
Grand Total.....	312	1013

condition at the time of injection. They represented, in general, a fairly representative cross-section of the indigent found in a large city hospital.

Rate of Injection.—In general, an average rate of 300 to 500 cc. per hour (about 5 to 8 cc. per minute) was maintained. With solutions containing 2.5 per cent of amino-acids, the amount injected in an hour was, therefore, roughly, 8 to 12 Gm. If this rate were continued for 24 hours, between 200 and 300 Gm. of protein nourishment could be thus administered, although the volume (8 to 12 liters) would be excessive. In a few cases the rate was greater, up to 500 and 900 cc. per hour of the 2.5 per cent solution. The largest amounts of Amigen were given as 5 per cent solutions (see No. 7, Table I). In two of these patients, 300 Gm. of Amigen (with equal amounts of glucose) were injected each day for three days, by means of a continuous venoclysis. Recently, a patient inadvertently received 1,000 cc. of 10 per cent Amigen in less than an hour; however, it had been neutralized to a pH of 6.5 by the addition of NaOH. Aside from abdominal pain, nausea, and vomiting there was no untoward result of this excessive rate of injection.

Most patients received but one or two liters of the Amigen solution. The most seriously ill were given more; the largest amount given to one patient was 26 liters during the course of ten days. In the two patients mentioned above, six liters a day were given for three consecutive days. We are unable to say how much more Amigen can be given per day as no attempt was made to increase the dose already mentioned, except that recently a patient received 25 Gm. of neutralized Amigen per hour for eight hours, with no reaction and considerable clinical benefit. Experimentally, we have injected without reaction as much as 140 Gm. of Amigen to a 10-Kg. dog in 24 hours, with insignificant loss of amino-acids in the urine; this would correspond to 980 Gm. in a 70-Kg. adult, or about 40 Gm. per hour, which is three to five times the rate we used in patients.

Findings.—The clinical effects of the Amigen injections were carefully observed in each case and detailed records made thereof. Table I shows the general distribution of some of the data.

Pyrogenic Reactions: Although chills and fever occurred in 15 instances, as can be seen by consulting Table I, ten of them occurred in patients receiving Solution No. 1; as already mentioned, this was the first solution employed and contained pyrogens in some of the distilled water used in its preparation. Of the remaining instances, three occurred in two medical patients, one with an acute respiratory infection, the other a severe osteo-arthritis; both patients had had chills previously. Of the remaining two instances, both had chills but no fever and thus really should not be classed as pyrogenic reactions. On the other hand, at least one of the patients in this series had chills and fever following a transfusion before receiving Amigen. From this analysis, it seems fair to conclude that the few observed pyrogenic reactions (chills and fever) were not produced by Amigen, and that solutions which are not pyrogenic produce no reactions on the addition of Amigen thereto.

Other Reactions: Two instances of urticaria were observed, one in a pa-

tient known to be allergic to various substances. Since allergy may be due to nonprotein materials, we may explain these two instances on such a basis, *i.e.*, to amino-acids or possibly mineral elements in the hydrolyzed casein. In both patients, the skin lesions responded to adrenalin and were followed by no sequelae. Flushing of the skin occurred in several patients, probably due to the specific dynamic effect of the amino-acids, which has been noted by other observers. As to temperature elevations, most of our patients were already suffering from fever before the amino-acids were injected, or were expected to develop fever as a result of the operative procedure. Study of these cases failed to show that Amigen was responsible for any significant temperature elevations. In many instances, the known specific dynamic action of the amino-acids, themselves, may have provoked some fever inasmuch as Shohl and Blackfan² found that the temperature elevations produced in infants by pure crystalline amino-acids and by hydrolyzed casein were alike. The chilly sensations observed in a few cases were, perhaps, also due to a specific dynamic action. Indeed, in two out of three cases in which the test was made, the basal metabolic rate increased during the course of the Amigen injections. Nausea and vomiting were rare in the present series; indeed, when expected as post-operative manifestations, Amigen seemed to minimize them. However, such symptoms are associated with the rate of injection; when Amigen is injected rapidly abdominal pain, nausea, and vomiting have been observed by Farr, Emerson, and Fletcher.³ In the patient mentioned above who received 100 Gm. in less than an hour, these symptoms occurred, though there were no other untoward effects.

Phlebitis: Careful observation revealed no instance in which 2.5 per cent Amigen caused any more phlebitis than similar solutions containing glucose alone. More recently we have prepared a neutralized Amigen solution (pH=6.5) which in stronger concentrations (5 and 10 per cent) seems less likely to produce phlebitis than similar solutions at a pH of 4.5.

Deaths: Careful analysis of the deaths in this series of cases revealed no instance in which the Amigen could have been responsible. In each case the patient was in a critical condition before the administration of the amino-acids. They were given in these patients because they proved of such definite help in other similar cases which recovered. These were patients with serious gastro-intestinal disease, in poor nutritional and general condition, a situation which is not uncommon among the indigent.

Therapeutic Value: Detailed objective evidence that amino-acids, when given intravenously, have a definite therapeutic value, was published in a previous paper from this clinic.¹ It was shown, for example, that excellent utilization of the injected material was achieved first because nitrogen retention was marked and persisted even during two weeks of therapy and second, because significant increases of the plasma protein concentration took place. Such detailed observations were not made in the present study. However, from the purely clinical point of view, there was ample evidence of the beneficial, even dramatic, effects of Amigen. In many cases it seemed clear that

the addition of the amino-acids to the parenteral glucose, after serious operations, tipped the balance in favor of recovery, although such impressions are, of course, difficult to prove. Significant was the fact that many patients volunteered expressions of subjective improvement in their general sense of well-being and strength, and this was confirmed by their clinical appearance and by the usual bedside observations.

It might be well, at this point, to make a few general remarks concerning the subject of protein deficiency. The practical application of this new method of parenteral protein therapy will be realized to a large extent by our ability to recognize protein deficiencies in surgical patients. The value of glucose is taken for granted because it supplies calories; yet body fat and tissue protein can likewise supply calories.

But there is no substitute for protein; indeed, one might say that if there is any secret of life it is bound up with protein which is the basis of all living protoplasm. In the past we have been lulled into a false sense of security about protein needs because of the presumed "stores" of protein in the body. Recent evidence has cast doubt on the practical application of this assumption. For example, it is now known that depletion of plasma albumin begins immediately after protein intake is stopped. Indeed, though hypoproteinemia is the only protein deficiency which can be recognized and measured clinically, its frequency is now generally admitted. Undoubtedly, other tissues suffer when their protein is depleted. The liver comes to mind, and something is known of this.^{4, 5, 6, 7} Manifestations of protein deficiency in other organs will doubtless be detected as time goes on. Indeed, one may even go further and say that certain acute conditions, such as burns, severe hemorrhage, shock, *etc.*, are in reality examples of acute protein deficiency since they lead to acute hypoproteinemia which the body cannot correct rapidly enough, and because fluid containing protein (plasma) is so therapeutically effective.

Plasma as a protein-containing fluid has become widely recognized within recent years as an important method of replacing lost protein, though it was used first in severe burns⁸ at the St. Louis City Hospital in 1935. As a means of supplying protein nourishment, though plasma leads to positive nitrogen balance in humans as shown by Kremen, *et al.*,⁹ it has two possible disadvantages. First are practical limitations; for example, the largest amount of protein which was given in 24 hours in the present study (300 Gm.) would require over 4,000 cc. of plasma or at least 16 donors a day. Second, are theoretical factors, *i.e.*, plasma replaces lost protein in the blood only, but must be hydrolyzed to amino-acids or small polypeptides by the body before it can be utilized by other tissues. In contrast, amino-acids injected intravenously are immediately available to all tissues. Indeed, if protein synthesis is rapid and much evidence seems to indicate that it is, an appropriate mixture of amino-acids should be built up into plasma proteins quickly enough to supplant in part, at least, the need for plasma and transfusions even in acute conditions, such as severe burns and hemorrhage. Work along this line is now in progress.

SUMMARY

Observations have been made of the injection of 1,013 liters of glucose solution containing a mixture of amino-acids (Amigen) in 312 patients. The injections were well tolerated and gave ample evidence of clinical benefit. Only two instances of urticaria were observed. The intravenous injection of a properly prepared solution of suitably hydrolyzed casein into the human in amounts averaging 8 to 12 Gm. per hour for an average-sized adult is a safe procedure, and is the most simple and convenient way of supplying large amounts of protein nourishment parenterally. The far-reaching implications of this new method of therapy are briefly discussed.

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EPITHELIAL HEALING AND THE TRANSPLANTATION OF SKIN*

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STUDIES of epithelial healing and of the transplantation of skin have been made in close association with the clinical picture of the requirements and possibilities of repair in a large number of patients over a 17-year period. The reasons for wound healing or failure of healing, the spontaneous repair of donor sites of grafts, the behavior of homografts and many other points have been studied by microscopic sections of the tissues involved. Laboratory animals are not very similar to the human in skin and subcutaneous arrangement, and it is thought that human biopsies have been of the most direct value. The record has proven interesting and instructive and it is hoped that it may help furnish a histologic and physiologic basis for further investigation. To Dr. Nathan Womack, thanks are given because of his help, interest, and patience in the protracted observations.

SPONTANEOUS HEALING OF LARGE OPEN WOUNDS

Wounds heal spontaneously by contraction of the surrounding edges, by filling in with fibrous tissue, and by scar epithelium going across from side-to-side. Skin is a complex organ and the epithelium is the only part of it that regenerates. The pad of derma that is really important in giving bearing protection does not regenerate, to any noticeable degree, and when a claim is made that a chemical will produce healing without scarring, the healing process is apparently not understood.

The thin scar epithelium that creeps across a wound by itself, and without any pad of derma to attach it to the subcutaneous tissue, may not be very serviceable as a bearing surface. It is thin, has no papillae, no hair follicles, no glands, and may form an excessive layer of keratin with nuclei remnants present far out in it. The latter finding may be evidence of a short life cycle of the cells associated with the continual wound stimuli of tension and repeated trauma. This scar epithelium may never become very firmly attached to the underlying fibrous tissue, so that large areas of it can be detached and lost by trivial injuries or infections (Fig. 1).

Failure of healing may occur and is seen most often in circular burns of the extremities and wide open areas on the scalp. In such extremities there

Failure of healing may occur and is seen most often in circular burns of the extremities and wide open areas on the scalp. In such extremities there may be little or no upward growth of epithelium from the lower skin edge, so that the presence of even a narrow longitudinal strip of skin may be a big

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help in spontaneous healing. In the scalp, it has been conjectured that the follicles are so far differentiated into hair-forming structures that they do not revert to the production of surface epithelium so easily as elsewhere in the body. This is not true in the face, however, where rapid healing occurs, even

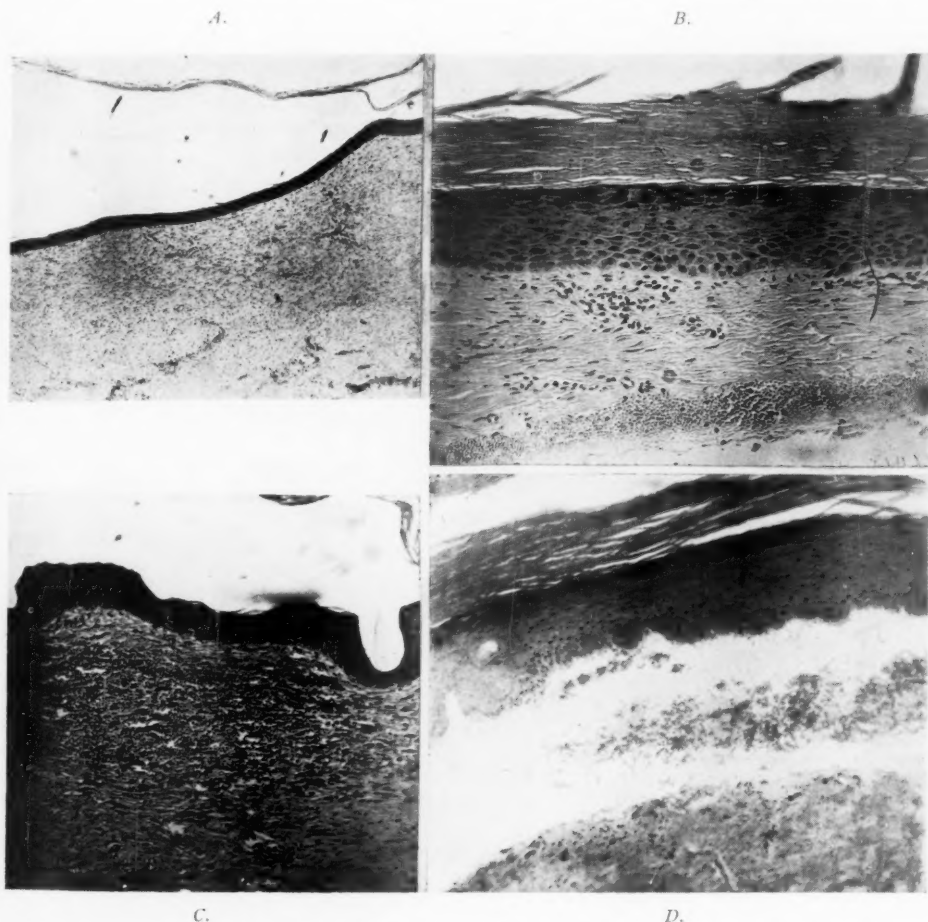


FIG. 1.—(A) Typical scar epithelial healing, with no dermal pad to attach it to the fibrous tissue under it. (B) Same thing existing in a scar after 20 years. This does become "tougher" but retains the same microscopic appearance. (C) Fresh scar, with red blood cells collected interstitially, just ready to detach the surface scar epithelium. (D) Microscopic appearance of the frequent gross finding of detachment of scar epithelium by hemorrhage. Even slight trauma may cause a large surface loss from hemorrhage under this poorly attached epithelium.

in full-thickness losses, presumably from deep hair follicles that extend clear down into the subcutaneous tissues (in men) (Fig. 2).

Individual variations in the growth of epithelium, aside from general nutritional factors, are marked. An occasional patient will heal a wide full-thickness loss and even get permanent bearing function. Others may heal rapidly but with so much dense, deep, fibrous scar that marked deformities are produced. These patients give about the most trouble of repair of any,

as this deep scar may have to be removed to allow normal function. Other patients seem not to grow any epithelium and may linger on over long periods, developing more pain and losing more body fluids all the time, and may die.

Studies of open wound (ulcer) edges have followed from the above considerations, and one of three pictures is usually found in them: (1) There may be no activity apparent at the edge at all, the epithelium simply thinning out and the stratum granulosum appearing to curve around to meet the basal layer, as though a permanent condition of open edge were to be established. This might be taken to illustrate an absence of response to the wound stimulus of the open area and usually occurs where there is little fibrous tissue laid down.



FIG. 2.—(A) Failure of healing in complete, circular full-thickness loss. (B) Edges quiescent, no growth from lower edge. (C) Complete healing following one thick split graft operation.

(2) There may be excessive keratosis with epithelial debris piled up along the edges, indicating a response to the wound stimulus by the short life of the cells, but failure of them to go on across the defect and effect a closure. (3) There may be a breaking up of the cells with apparent invasion of the deeper fibrous tissue, and it is presumably in this type of reaction that carcinoma develops. Carcinoma develops infrequently in comparison with the numbers of burns that occur. It occurs most often in areas that are prevented from collapsing, such as the scalp, or in large, dense fibrous ulcers that are repeatedly broken open.

Deep fibrous healing is presumably the only mechanism by which defects below the skin level may finally become closed, the area filling with granulation tissue that gradually changes to fibrous tissue. This dense tissue tends

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at times to defeat its own purpose by becoming so thick and avascular that it cannot support its own surface or any epithelium struggling across it. In some old leg ulcers, calcium may even be laid down in the scar and resemble sequestra roentgenographically. (This, of course, may come from adjacent periosteum.) It is the failure to remove this deep scar that accounts for many of the failures of grafts for leg ulcers and other wounds that have been open for a long time. Because of the thick, deforming dense fibrous tissue that may go along with rapid epithelial growth and produce early distortion, it is sometimes easier to repair the patient who makes little if any epithelial effort of his own, but who at least does not go into every possible kind of deformity.

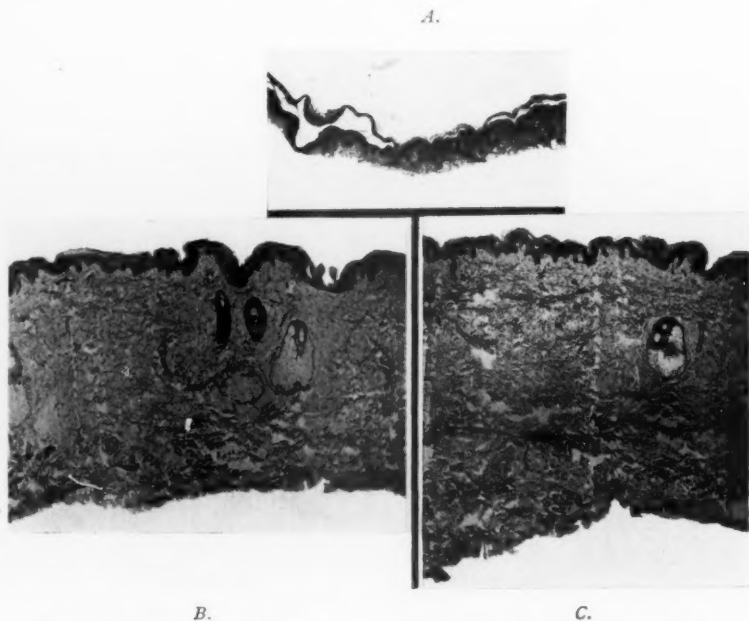


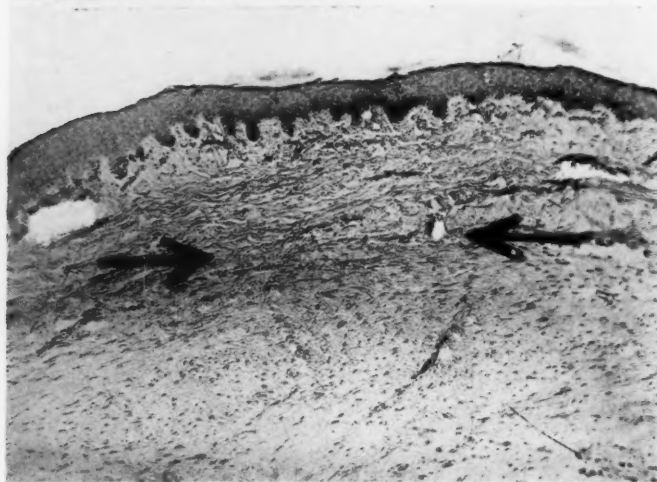
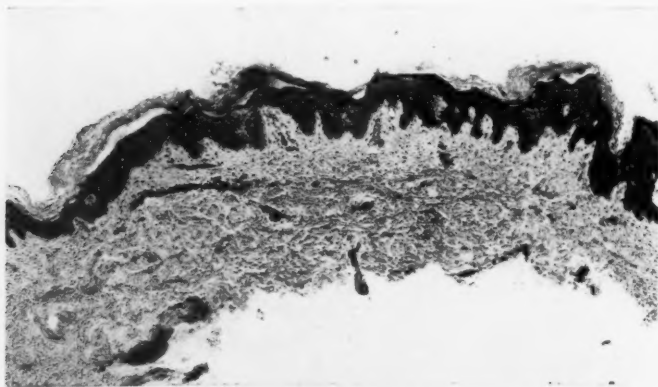
FIG. 3.— Three Types of Skin Grafts: (A) Ollier-Thiersch graft, with practically no derma. (B) Thick split-graft of about 80 per cent of the full-thickness. (Used in 1932.) (C) Full-thickness graft.

Generalized skin shortening is a term applied to areas that have healed, possibly with satisfactory surface, and which show no gross deformity but which do not permit normal function of complete flexion and extension. This is due to deep scarring and insufficient skin and is comparable to clothes that are too tight—the patient simply cannot bend around in his skin-envelope. The situation becomes especially bad if he puts on weight, as the dense blanket of scar will not distend for the new fat, and at times this thick, unyielding surface actually seems to form bursae over the deep fat. Notable examples of this have been published—one patient could not raise his arm without raising his leg, and another had not sat down normally for 26 years. The repair consists of opening suitable areas, either stretching back the edges or removing scar that is too dense, and filling the defect with free skin grafts.^{2, 9}

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Early Skin Grafting of Burns and Other Open Wounds.—The main interest, generally, perhaps, is the problem of massive defects due to burns that have to be grafted to save life and prevent deformity, and in the later repair of contractures and deformities. Burns can usually be made clean enough for

A.



B.

FIG. 4.—(A) Thick split-skin graft used successfully in repair of a burn. (B) Biopsy of same graft one year later. Arrows point to attachment of normal dermal pad to deep tissue. May be compared with Figure 1.

grafting in 20 to 30 days and, as this plan has been followed for a long period, it can be extended now in war wounds, if suitable preparation can be carried out and tanned membranes gotten off early enough.

The immediate excision of burns and grafting, as suggested by Murat Willis many years ago, may have isolated applications, but cannot be a routine procedure for all burns. It would result sometimes in much good

tissue being sacrificed or in not getting rid of enough burned tissue and, because of this, a loss of the graft.

Thick Split-Skin Grafts and the Relative Thicknesses of Other Types of Grafts.—Figure 3 shows these grafts all taken from the same area in the same patient and magnified to the same degree. The split-graft is about 80 per cent of the full-thickness in this instance. When large areas have to be resurfaced, it is necessary to utilize only partial-thickness of the donor skin, leaving behind some derma containing portions of hair follicles so that healing can occur. When the full thickness of the skin is not taken, then it has been split in two and the most appropriate name for this type of graft seems to be "thick split-graft." The original Ollier-Thiersch graft was too thin to be of much value, but almost any operator would, automatically, cut thicker grafts as he progressed in the work, so that the usual graft now used is one-half to three-fourths of the full thickness of the skin. Various other names have been employed to describe this graft.

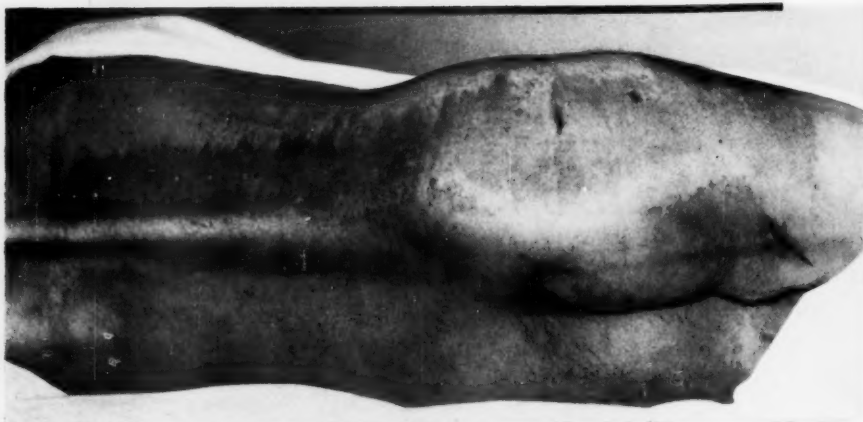
The actual thickness of whole skin varies greatly in age, sex, race, various degrees of nutrition, and in different areas of the body. The skin is also of different character in various areas. On the back, for instance, the epithelium is relatively thin but the derma is so thick that full-thickness grafts from this area can hardly be counted on to survive. Burns in this location are seldom completely through the derma and tend to heal readily. Split-grafts from this area do not need to be as thick, relatively, as from other areas, and because of this, as many as five "crops" of skin have been taken from the same donor site at intervals as short as 19 days. The palm is just the opposite, with a specialized type of epithelium that produces a thick keratin layer for protection and has a thin derma without hair follicles. It heals very poorly following burns and even rather superficial ones may produce marked deformity, especially in children. The same is true of the sole.

Importance of the Dermal Pad of a Skin Graft.—To show the importance of a pad of normal derma between the underlying base and the surface epithelium, the split-graft in Figure 4 A was followed clinically for one year, at which time the result was satisfactory, and a biopsy was taken. Figure 4 B shows the graft after one year, appearing as normal skin with normal papillae, no excessive keratin—indicating a normal life cycle of the cells and absence of wound stimulus. The epithelium is attached to what is left of the fibrous base by the pad of derma included in the graft and a normal bearing-surface is produced that can withstand the usual trauma of getting around. This may be compared with Figure 1 A and B, in which the scar epithelium on a scar base is seen, and the comparison is the essential difference between spontaneous scar epithelial healing and healing by grafts.

Cutting Thick Split-Skin Grafts.—These grafts may be cut in several ways, the main essentials being a long sharp knife and some method of producing a diaphragm on which to cut. The diaphragm may be produced by pressing down, as with two large spatulae, or lifted up, as with tenacula, a vacuum suction retractor, or with glue, as on the dermatome. Each method has its

advantage, according to the availability of the skin in relation to size and nutrition of the patient. For large defects, the grafts should be cut as large as necessary for ease of repair—on a large person, ones 18x5 inches are possible, and grafts 36x4 inches have been cut free-handed with a long knife (Fig. 5 A, B). The dermatome may be useful in obtaining smaller grafts from more difficult areas, such as over the thorax, or from small children, where its size (8x4 inches) may be sufficient. One has to be careful not to

A.



B.

FIG. 5.—(A) Free-hand method of cutting thick split-graft, about 75 per cent of the full-thickness (11 x 4 inches). (B) Larger grafts are available in large patients. Healed sites shown of one graft 36 x 4 inches, and one 30 x 4 inches.

set it so deep that the full thickness of the skin is taken, or so thin that the graft cannot be detached from the drum. The free-hand method, when possible, is usually the fastest and safest method, and with some practice the thickness of the graft can be graduated and certain designs roughly obtained (Fig. 5 A).

Preparation of Base for Split-Grafts and Where They Will Grow.—Grafts may be put directly on the surface of open wounds if the granulations are bright red, flat, firm, and not edematous. However, if feasible, the granula-

tions are *sliced* cleanly off with a graft knife. They are not scraped, as this seems definitely to interfere with the take. In healed areas, especially if they have recurrently broken down, the scar epithelium and deeper fibrous tissue are removed down to a thin scar base so the area can relax. It may be necessary to open entirely through the scar to gain correct position of the parts, but this should always be done very carefully if there is any possibility of exposing tendons by sudden force. In Figure 4 B, the deep scar that has been left is seen under the graft.

Grafts will not grow on tendon or bare cortical bone (without periosteum), but may carry a lateral blood supply of their own across small areas of these tissues when exposed. This is important in work about hands because, if one goes very carefully, one can stop any tendon exposure before it is over 1 cm., and this is about the limit that the graft can be expected to carry over.

When put on fat or muscle, or uneven scar bases, the grafts will grow, but will later show every irregularity and there will be new scar tissue laid down that may contract the surface markedly. This has been said to be due to contraction of the graft, but it is probably from contraction of the bed under it.

Sulfanilamide may be dusted sparingly over the bed for the graft without measurably stopping the growth, but any excess certainly would be contraindicated and it cannot be expected to replace any precaution of cleanliness nor to prevent loss of a graft if a severe contamination has occurred.

The preliminary preparation is as important as any step in the repair of a large open wound and consists mainly of open drainage, soap and water, local sulfonamides, and daily débridement. Rest, elevation, and pressure dressings are fundamentals that cannot be omitted, but are only mentioned here for the sake of completeness. Ointments on areas to be grafted are used on fine-mesh gauze during the preparation but none should be on the wound at the time of operation, and if suspected, ether should be used as a solvent. Grease left under a graft almost precludes its growth. Somewhat of a reason for this has been noted (by others) in tissue cultures, in the finding that on the addition of a drop or two of mineral oil to a tissue culture, taxis of the cells ceases.

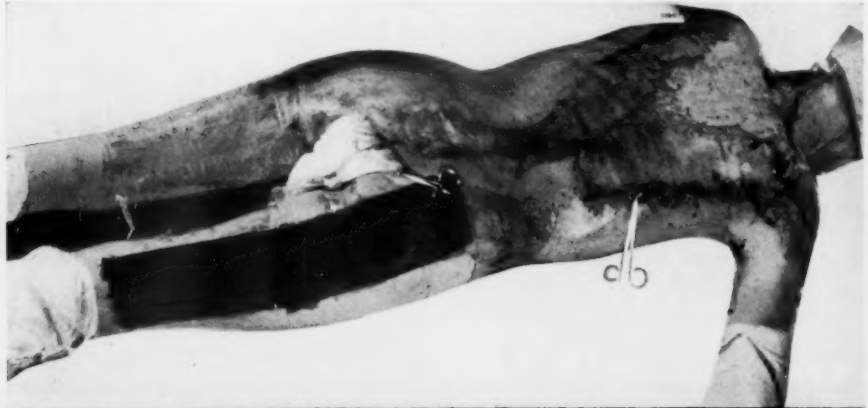
Pressure dressings on skin grafts are almost an absolute necessity (an occasional graft laid on and not protected might survive, but one could not run a service that way.) The medium of pressure distribution that seems most suitable is white cotton mechanic's waste. It has to be held on the same as any medium does and it is, therefore, the final bandage that produces the pressure (Fig. 6). Firm pressure is an excellent antiseptic, apparently by preventing the accumulation of surface fluid and keeping down edema, and its use has been noted in the hieroglyphics of the Edwin Smith Surgical Papyrus. Pressure dressings are also used on fresh burns when possible.

EPITHELIAL HEALING

The Epithelial Healing of Donor Sites of Thick Split-Grafts.—This provides an especially good opportunity for gaining information of epithelial

healing in general. Large areas are denuded under sterile conditions and the influence of any agent on the rapidity of epithelial healing can be readily noted. The resemblance to a superficial burn or to a deep abrasion is evident. The ability of these to heal promptly makes possible the transfer of 100 to 250 square inches of skin at one time, and it is most important to make sure that

A.



B.

FIG. 6.—Fine-mesh gauze next to donor sites and over grafts. Massive-pressure dressing, using cotton-mechanic's waste to protect both donor sites and grafts. Massive, thick split-grafts, 210 inches in one operation. One graft, 16×4 inches, from shoulder to buttock. Others over back, arm and neck.

this healing does occur by using extreme care in dressings and protection (Fig. 6).

Dedifferentiation of the Hair Follicles in the Healing of Donor Sites.—In the healing of donor sites, the deep glandular epithelium in the derma spreads out over the surface and entirely recovers it in six days, and in six more days, dressings can be left off. In fact, only one dressing is done on the tenth to the twelfth day. This process is a sort of "dedifferentiation" of the cells of the hair follicles, as far as we have been able to determine, and a gross observation

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in substantiation of this is the fact that on the palms and soles, where there are no hairs, healing is slow.

Microscopic Appearance of Epithelial Dedifferentiation.—The whole process can be studied microscopically in biopsies taken at intervals (Fig. 7). Healing is complete by the sixth day, and by the ninth day, conversion to squamous epithelium is so complete that papillae are formed and some keratin

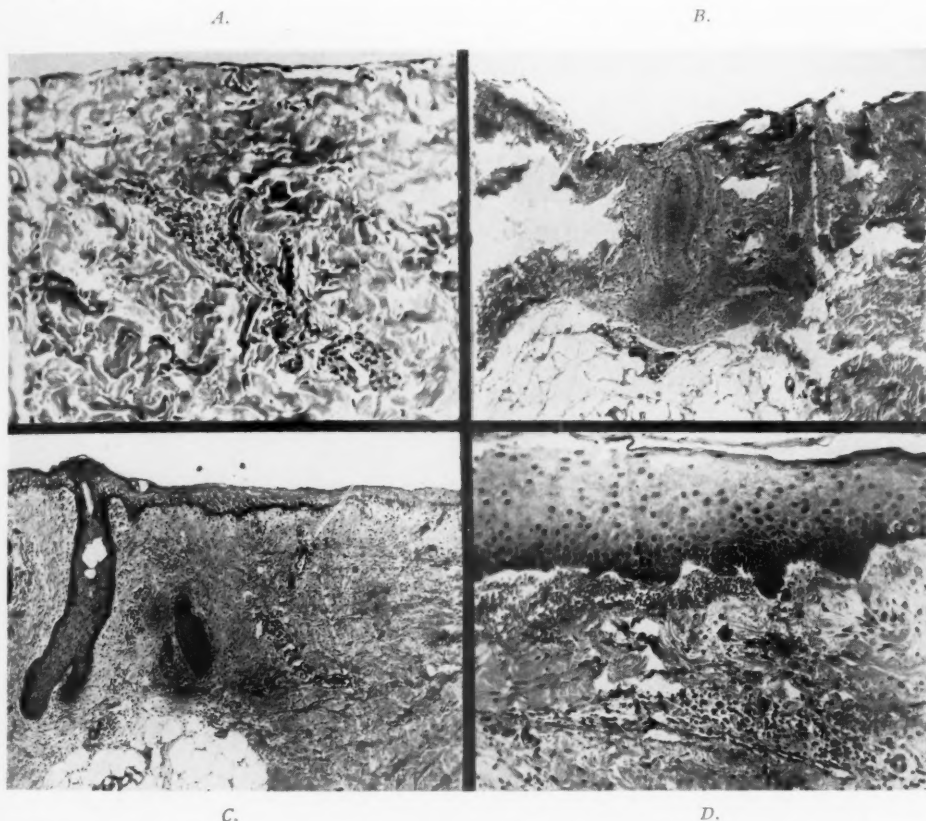


FIG. 7.—Healing of Donor Sites of Thick Split-Grafts: (A) Biopsy, two-day-old donor site—no surface epithelium. (B) Two-day-old biopsy showing deep follicle but no surface coverage. (C) Four days later, or sixth postoperative day, showing complete coverage with squamous epithelium. (D) Ninth day, with normal appearing epithelial surface.

is being thrown off. This process is apparently the reverse of the original formation of hair follicles. It is also something like a reversal of carcinoma formation, and it was thought that a somewhat similar picture might be found if enough healing donor site biopsies were done. This has not been entirely clearly shown because the cells go out so rapidly and orderly, but suggestions of it have been found.

Careful Protection of Donor Sites to Obtain Healing.—It is apparent that this process is a very delicate one and that irritation of any nature, chemical, bacterial, or mechanical, will prevent healing. When this does occur, the healing period is changed from ten days to eight or ten weeks, and whole

areas of the derma seem to melt away. It is evident that extreme care should be taken not to damage these cells and, therefore, no strong chemicals are put on the area. It is dressed immediately to protect it from trauma and contamination with fine-mesh grease gauze (No. 44 gauze), held firmly in place with overlying pads, adhesive and bandage that cannot slip. If any openings have been cut through the derma, they are carefully closed before the dressing is applied (Fig. 6).

When large areas are denuded, the additional bleeding and fluid loss may be considerable and whole-blood transfusions are often advisable.

The application of fine-mesh gauze to these and all raw surfaces is a fundamental of extreme importance to allow healing to progress smoothly and, on granulating surfaces, to avoid growth of them through the meshes of coarse gauze.

Rapidity of Healing and Multiple "Crops" from Same Area.—Split-graft donor sites usually have to be guarded a week or so longer after the 10 to 12 days, but a second "crop" of grafts has been taken as soon as 10 days after the previous "crop," and five "crops" have been taken from the same area. There is a marked variation in patients in their rate of healing. One patient, for example, who healed his donor sites rapidly and had four "crops" from the same area, did not make any new lateral spread of epithelium over his burns. Negroes are ideal patients for grafting; grafts seem to grow on them almost regardless of technic, but they are a little slower in healing their donor sites. This may be because they tend to have less hair.

The Skin of the Back.—This early and repeated healing where multiple "crops" are taken has usually been from the back, where the derma is thick, but care is taken not to cut too deeply; the skin does finally wear out and the last "crops" are not as nice to use as the first one.

The possibility of enough skin for repair in each burned patient is usually present if the above precautions are taken. The graduation of the thickness that is possible in free-hand cutting is probably the safest way of avoiding trouble, and of insuring the possibility of multiple "crops" from the same area.

Saving a good donor site on badly burned patients is important for obtaining smooth full-thickness grafts when final operations are to be performed about the face and neck. A thigh or the lower abdomen may be left for this work, but it is frequently found that someone has removed pinch-grafts right out of the center of these areas.

HOMOGRAFTS

Homografts are usually thought of at this point, when the possibilities of the patient having enough of his own skin are considered. These grafts will take almost universally even without regard to blood grouping. In grouping one series of 26 down into the M. and N. groups (with Dr. Francis E. Holfort) no relation was found either to the take or to the length of persistence. However, they will not persist in place over 10 to 11 weeks, and usually begin to disappear at the third week by a sort of solution of the graft, usually without pus formation.

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Biopsies taken early in this process of solution show interstitial edema, with slight cellular infiltration, as might be seen in an urticarial wheal. Later, the interstitial edema is less striking, and the cellular infiltration becomes heavy, consisting chiefly of round cells with many eosinophils and some polymorphonuclear cells. This heavy cellular infiltration coincides with the disappearance of the various dermal elements and epithelium in scattered areas. Grossly, the graft has numerous tiny areas of loss and appears "moth-eaten"

A.



B.

FIG. 8.—Emergency Dressing of Wounds in Homografts: (A) Extensive burns of arms, legs and face. (B) Whole arm healed with homografts from father. At same time, permanent autographs put on hand and face.

at this time. These areas increase in number and coalesce until final complete solution of the graft occurs. It would appear that the proteins in the homograft are antigenic and that the host requires about three weeks to build up a maximal allergic response to them. If a second crop of homografts from the same donor were applied to the patient at this time, one would expect almost complete failure to take. By the same reasoning, any previous attempts to "desensitize" the patient to the donor's skin proteins would probably decrease the chances of take. Conversely, attempts to "denature" the antigenicity of

the proteins in a homograft, or to change them by previous immersion in the patient's serum, have not proven clinically successful in skin grafts.

The emergency "dressing" of wounds in homografts is employed occasionally as a life-saving measure and in intractable children. Large sheets are taken from the donor and applied quickly, about as a dressing of the wound. The effect is stopping of pain; and the necessity of care, improvement generally, cleaning up locally, so much that there may be a marked stimulus in the patient's own epithelization, have been misinterpreted by some observers as a permanent survival of the homograft (Fig. 8).

According to Dr. Leo Loeb, no two individuals are exactly alike, and with our present knowledge, there is no use to expect a homograft to survive. Much work has been done along these lines, and if the problem could be solved, one of the greatest possible advances would have been accomplished. Skin is an organ and not just the epithelial element, so that it probably cannot be grown in a foreign body any more than any other organ and persist.

Homografts in identical twins, however, have been shown to survive, and if a twin were burned, the other one could probably be used satisfactorily.⁴

Delayed or refrigerated grafts are possible and have been used clinically occasionally, and experimentally in animals, and from humans to animals, but there is not much clinical use in the procedure at present, since the patient is always on hand to supply his own skin, and the obtaining of the graft is the minimal part of the procedure. In one case a successful full-thickness graft on the neck had been stored in an ice-box for forty-eight hours; as far as is known, this is the first clinical instance of the use of this procedure. One can conjecture all sorts of storage plans and tissue culture plans for grafts, to be used in war time, but final success has not been attained.

(Illustration of this part and eight other figures omitted.)

LATE COURSE OF THICK SPLIT-GRAFTS

Sebaceous collections may occur to an annoying degree, possibly because the cut glands secrete backwards. At least it appears this way since multiple large collections may develop. Their importance is that final healing may be delayed, and if the large collections become infected, excoriation or even loss of part of the graft may occur. There is usually a deep layer of epithelium under these collections, so that if they are opened and expressed, and any overhanging edges trimmed away before infection causes damage, serious loss is avoided. This occurrence is one of the marked variations, some patients not showing it at all and others showing it badly, regardless of how thick the graft is cut; however, full-thickness grafts never show it. This also may be due to small areas of the original skin being left behind and the grafts having been put over them.

Persistence of function of skin grafts over long periods of growth has been studied and it seems that grafts do grow or stretch out, so that if a graft has been successful at the beginning, it is apt to remain so. If any lack of skin for ease of function (skin-envelope) is noted, suitable openings can be made and more skin let in.⁹

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Satisfactory function of grafts is meant to include: "(1) Enough skin for free movement; (2) moderate looseness; (3) ability to withstand the usual trauma of getting around; and (4) the development of normal sensation. Full normal sensation usually develops in free skin grafts and is influenced by the amount of deep scar that is left and, of course, is dependent on the presence of sensory nerves in the area."⁹

Metaplasia of grafts (and flaps also) does not take place and, therefore, a really normal sole or palm, for instance, cannot be restored. The skin of

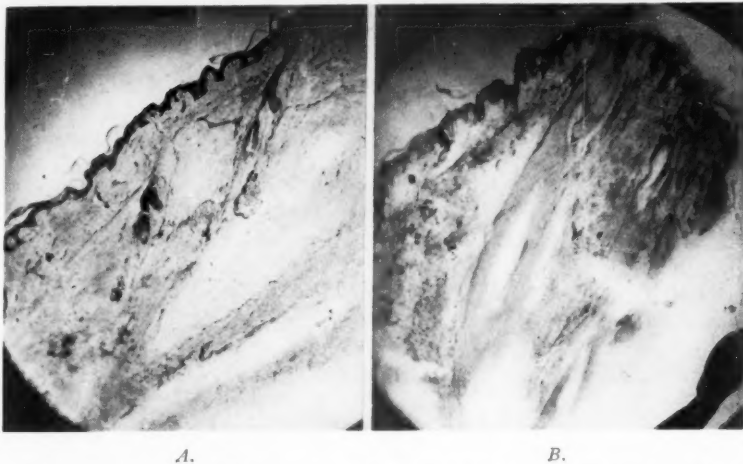


FIG. 9.—Failure of Metaplasia of Skin-Grafts: (A) Biopsy after one year—from graft in orbit. Graft is still skin, grossly and microscopically. (B) Biopsy after five years—from inside larynx. Graft is still skin, with hair growing from it.

each of these areas is specialized to the point of being an organ; the microscopic structure is different from birth and the peculiar bearing qualities are not developmental. "A graft or a flap on a sole may make calluses (or even annoying warts) but it will not metaplast into true skin or subcutaneous tissue of the area. They always have to be protected and the wart formation guarded against. If hair is transplanted, it will continue to grow, except that it may be worn off.

"Skin grafts transplanted to normal mucous membrane surfaces, such as the mouth, larynx, and eye socket, show no evidence of a change to a mucous membrane. The skin simply persists as such and even raises hair in these areas, if there are any functioning follicles in the graft" (Fig. 9).⁹

LINES OF INVESTIGATION.—At this time, when burns and grafts demand a good deal of attention, it is desirable to have the whole subject, including objects, reasons, possibilities and limitations, put on a plane approaching other surgical subjects. Important lines of investigation are: (1) Information to be gained and correlated from tissue cultures; (2) chemotherapy in relation to preparation of wounds and at time of operation; (3) refrigeration of grafts before being applied and of the areas after operation; (4) development of occlusive dressings that are transparent and removable; (5) prevention of

burns; (6) earliest possible replacement of skin following burns; (7) improvement in dressings and pressure media, and of air pressure on wounds plus burns; (8) simplification and ease of obtaining split grafts; (9) possibility of getting homografts to survive; and (10) utilization of delayed grafts.

Much has been accomplished, but it is apparent that there is room for vast improvement.

PREVIOUS PUBLICATIONS

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- ² The Repair of Surface Defects, from Burns and Other Causes, with Thick Split-skin Grafts. *South. Med. Jour.*, **28**, 408, 1935.
- ³ A Study of Ulcerations of the Lower Extremity and Their Repair with Thick Split-skin Grafts. *Surg., Gynec., and Obstet.*, **63**, 331, 1936.
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- ⁵ Restoration of the Entire Skin of the Penis. *Surg., Gynec., and Obstet.*, **65**, 362, 1937.
- ⁶ The Repair of Surface Defects of the Hand. *ANNALS OF SURGERY*, **107**, 952, 1938.
- ⁷ The Treatment of Burns. *Brennemann's Practice of Pediatrics*, Vol. 4, Chap. 52, p. 1, January, 1937.
- ⁸ The Covering of Raw Surfaces. *Internat. Abst. Surg.*, **67**, 105-116, August, 1938.
- ⁹ Persistence of Function of Skin Grafts through Long Periods of Growth. *Surg., Gynec., and Obstet.*, **72**, 848-853, 1941.
- ¹⁰ Thick-split Skin Grafts in the Repair of Burns. *Surg., Gynec., and Obstet.*, **73**, 265-267, 1941.
- ¹¹ Skin Grafting of Burn Deformities. (Army Manual, to be published.)
- ¹² Massive Repair of Burns with Thick-split Grafts. *ANNALS OF SURGERY*, **115**, No. 4, 658-674, April, 1942.

DISCUSSION.—DR. SUMNER L. KOCH (Chicago): There were so many things Doctor Brown could not include in this rather brief discussion, that I want only to emphasize just a few of the principles that he has suggested and repeat them, because we think they need to be repeated from time to time.

First of all, if there has been a whole-thickness loss of skin, no dressing will bring about healing. The only way that raw surface can heal is by ingrowth, the slow ingrowth of epithelium, or by replacement.

Second, the more quickly replacement is brought about, the less will be the contracture that develops. All of us, I am sure, see, too often, patients left for long periods of time in the hope that spontaneous healing will occur. While it does go on very slowly, difficult and serious contracture is developing and increasing and, of course, the longer it goes the more difficult it is to overcome.

Third, Doctor Brown has not had time to talk about the importance of securing a clean field. He has suggested it, and he has referred to it in his paper, but to secure a successful result one must have a clean field. Many advances have been made recently, particularly in methods of securing grafts, and all of us have seen very beautiful grafts taken by various methods. Too often the unthinking surgeon forgets that the field has to be clean or the graft cannot live. Nothing that I know of helps so much to secure cleanliness of that field as simple surgical cleanliness and avoiding adding infection to the raw surface that is to be covered.

Again, surgeons so often forget the importance of not adding infection to the open wound as they are trying to transform it into a clean wound. They forget that the more serious potential sources of infection are the surgeon's hands and his instruments and, most of all, the uncovered mouth and the unmasked nose. I never have had the opportunity of going to another hospital to see a patient with an extensive injury and been offered a mask to cover my face before examining the large wound that was distressing the surgeon. I

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think it is something that we have to repeat over and over again to our students and our house officers, that just as in the operating room, where everyone admits the importance of preventing infection, so in the ward and in the patient's room those same precautions must be taken, and that if we are going to secure clean wounds we must prevent adding infection to them throughout the course of treatment.

DR. NATHAN WOMACK (St. Louis): There is one thing about Doctor Brown's paper that I would just like to stress, and that is his demonstration of the extraordinary rapidity with which apparently perfectly normal epidermis can be formed in five or six days from squamous epithelium. If it is sectioned longitudinally and separated with a clothespin, one sees a very marked resemblance to skin, but functionally it does not resemble skin. It does not resemble it in pigmentation. It does not resemble it in its metabolism.

It will be very interesting to observe what happens to some of these donor sites that Doctor Brown has under observation many years from now, whether or not the function of the stratified squamous epithelium of the skin is picked up as well as its morphologic structure.

One other thing: I think the preservation of potency we see explains the marked variation that one sees in the other direction; that is, the formation of tumors.

The fact that cells are able to perform other functions than those they are normally supposed to do, such as squamous epithelium in the bronchus, and squamous epithelium in the gallbladder, explains some of the multitudinous morphologic experiences and some of the skin cancers that Doctor Brown has been talking about.

DR. VILRAY P. BLAIR (St. Louis, Mo.): May I emphasize a point that Doctor Brown brought out? I did not catch that he said it directly, though he demonstrated it. That is the futility of homografts in preserving the vitality of the patient and bringing about an early condition where one can put on the autograft. Especially in young children, that is very useful. A child is badly burned. You take the graft from the mother and put it on, knowing it is not going to last, but by the time it has disappeared it has fooled many people into reporting in the literature that they have had permanent results, which I do not believe they ever did get.

SKIN REMOVAL IN RADICAL MASTECTOMY*

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THE SURGICAL TREATMENT of cancer of the breast was in a quite unsatisfactory condition until 1894, when Halsted and Willy Meyer published their papers on radical mastectomy. Halsted advocated "wide" excision of skin with removal of the breast, the pectoralis major and minor, thorough dissection of the axillary lymph nodes, and immediate skin graft. This had a profound influence on the surgical treatment of breast cancer. His original operation has been followed by many to this day, even though Halsted later somewhat changed his own technic.

In the decades that have since passed, there has been quite a general acceptance of the complete removal of the breast, the thoracic portion of the pectoralis major, the pectoralis minor and the axillary contents. There has not been, however, an agreement on the best method of treating the skin over the breast.

Halsted advised the "wide" removal of skin of the breast including the nipple and areola. His method seemed to indicate an incision through the skin down to the deeper subcutaneous tissue, followed by peripheral dissection to expose all of the breast along with the muscles and axilla. He then carefully closed off the dead space in the axilla with interrupted silk sutures, to leave a raw area that was covered by immediate skin graft. Halsted had operated upon 50 such cases when he made his report in 1894. Of these 50 cases, 31.9 per cent developed local recurrences.¹ From a review of the literature, the writer has been unable to find any statements of the measurements of the skin removed.

Handley,² in his study of cancer of the breast, had come to the conclusion that the growth spread chiefly by permeation and lymphatic emboli. He contended that the cancer spread in a ringworm-like process in the deep subcutaneous level just superficial to the fascia over the muscles, and that it was only in a late stage that extensions from this level went up vertically to the skin, like a bubble coming to the surface of a pond. He felt that there was no spread by permeation beneath the cutis. Therefore, he believed that it was not necessary to sacrifice a "wide area" of skin such as Halsted had advised, but that a smaller area could be excised with wide peripheral dissection in the subcutaneous level, superficial to the deep level in which the cancer spread by permeation. In accordance with this observation, he was content to remove a diameter of four to five inches of skin by a circular incision, with the tumor as the center. He was usually able to approximate the skin edges by a plastic type of repair at the completion of the operation. In this way he avoided the skin graft to the bare chest wall.

* Read before the American Surgical Association, Cleveland, Ohio, April 6-8, 1942.

SKIN REMOVAL IN MASTECTOMY

It is accepted that cancer of the breast begins as a local lesion, and that it first spreads by *infiltration*. Undoubtedly, in some of our cases this was the only stage that the growth had reached. But because of our known inadequate methods of gross and microscopic examination, it has been felt necessary to perform a radical mastectomy. The next steps in the spread of the growth have been by *permeation* and *lymphatic embolism*. Both these methods probably occur at the same time, but vary in incidence and degree, if one is to judge by clinical and pathologic experience. For it is known how variable is the relationship between primary growth and axillary metastases. Fortunately, *blood embolism* does not occur often, otherwise there would be little indication for more than local surgery.

All these methods for the spread of breast cancer are accepted in principle, and there has been but little disagreement except on the subject of permeation. As I see it the "Halsted school" believes that the cancer spreads by permeation in the cutis, and that, therefore, a "wide" portion of skin must be removed. Secondly, we have a school of thought, led in New York by Hugh Auchincloss, that agrees with this Halsted school but believes that it has not gone far enough, as the spread peripheral to the excised skin is in the tissue immediately beneath the cutis. Therefore, such a careful dissection of the skin must be made as to leave no fat attached to the under surface of the skin. And thirdly, we have the Handley belief that the cancer spreads in the deep subcutaneous tissue, so that when the skin or immediate subcutaneous tissue is involved, it is due to involvement of vertical lymphatics to the skin from the deep tissue.

The pathologic evidence for each belief has been difficult to establish so that different opinions have been able to persist. On clinical grounds, however, one may draw some conclusions. The proponents of these theories have enthusiastically gone into battle to prove their contentions. The Johns Hopkins Hospital report claims that, in every way, wide excision with skin graft gives superior results to the plastic closure technic. Auchincloss³ states that with his more radical technic, "local recurrence is rare." Handley,⁴ in 1930, said: "Broadly speaking, local recurrence was nearly abolished."

Freedom from recurrence, or persistence of the disease in the local area, is said to be a good measure of the thoroughness of the radical procedure. Evidence of the disease beyond the field is no reflection on the surgeon's technic.

In the case of local recurrence, one must presuppose that malignant cells have been left in the skin and in the raw area, with a chance to grow and later appear. On the other hand, one must also admit that by lymphatic embolism, cells may be deposited in the intercostal lymphatics to spread locally. In the same fashion, the lymphatic emboli may go, and I believe frequently do go, to the lymphatics associated with the perforating branches of the internal mammary artery. So it seems to me that some of these nodular recurrences in the intercostal space near the sternum, and occasion-

ally some of the others deep beneath the skin, have no part in the proof for the indications for skin removal.

Local recurrences in the scar and the skin of the immediate chest area are of great significance. But when they appear in skin edges after a 25 cm. diameter of breast skin has been removed, how shall we judge it? Was the case inoperable primarily—or, when the recurrent nodules appear in the local skin after ten or 15 years, along with lung or bone metastases, is this due to a faulty lack of sufficient skin removal?

It is the fashion in some circles to decry "statistics," as unworthy of notice because of the variabilities in the nature and course of cancer of the breast. It is admitted that one cannot argue from the general to the specific in each case. It is also true that dogmatic traditional statements of procedure should not be accepted on mere impressions. The collection and study of the operation, the pathology and the postoperative course of patients over at least five years, gives an indication of trends and indications for procedure that are worth while.

For this study the writer has taken the records of the cancers of the breast that have been subjected to radical mastectomy at the Roosevelt Hospital in the period January 1, 1922 to December 31, 1936. For the purpose of this review, all cases that had recurrence in less than 5 years, and later, were included. All cases that were well and free from the disease but lost in less than five years were excluded. In some of the articles in the literature, on local recurrence, the authors have included too recent cases. No time was allowed to develop recurrence.

This is a report of 254 cases, 238 with plastic skin closure, and 17 with skin graft.

Of the 238 plastic skin closures, 137 had proven axillary metastases, 43 had local recurrences, including three parasternal nodule recurrences (31.5 per cent).

Of the 238 plastic skin closures, 101 had no axillary involvement (in pathologic examination). Eleven had local recurrences, including four parasternal nodule recurrences (10.8 per cent).

Total—238—54 local recurrences (22.6 per cent), excluding seven parasternal recurrences (19.7 per cent).

Of the 17 skin graft cases, 14 had axillary metastases, with five local recurrences (35.7 per cent), while three had no axillary metastases, with one local recurrence (33 per cent).

TABLE I
PERCENTAGE OF RECURRENCES IN 238 CASES WITH PLASTIC SKIN CLOSURES

No. of Cases	Local Recurrence	Per Cent
137 with axillary metastases.....	43	31.5
101 without axillary metastases.....	11	10.8
Totals 238	54	22.6
225 graft cases (Johns Hopkins Hosp.).....	79	35

SUMMARY

The writer, together with his associates, had been intrigued by the work of Handley. It was felt that the plastic closure was preferable to the skin graft if it did no harm to the patient. In the period included in this paper, the policy of following out Handley's technic has been followed. It will be noted that in 17 cases immediate skin graft has been necessary. This is due to the fact that we insist on removal of at least 15 cm. of skin at the narrowest diameter, and often more if the growth was large. By liberal undercutting, it is usually possible to approximate the skin without undue tension, but in the patient with small breasts this may not be feasible. On the contrary, it is easy to close skin edges primarily in large breasts, even though a diameter of 25 or 30 cm. has been removed.

We wish to emphasize the fact that in the cases with local recurrence death was not caused by the local recurrence but by the cancer metastases outside the operative field. Furthermore, in the late skin recurrences, we have been impressed by the simultaneous appearance of evidence of cancer outside the operative field. For this we have come to the conclusion that we have not lost any patient because we have failed to make a wider excision of skin.

We feel that the "skin graft school" has taken an empirical attitude that is not supported, as yet, by results.

CONCLUSIONS

From our investigation we have come to the conclusion that (1) local recurrence is fairly frequent; (2) a follow-up over many years will show increasing percentage of local recurrence; and (3) our method of skin removal is reasonably radical. In the local recurrences (especially in the skin) that occur with this method, the failure is not due to the method but to the pathologic fact that the cancer is already widespread, without our knowledge, and beyond the reach of surgery.

A comparison of our results with those of other "schools" is difficult because of the paucity of information on this subject in the general literature. A notable exception to this has been the exhaustive study of the Johns Hopkins Hospital cases by Lewis and Rienhoff. Reference to this report is made in Table I.

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TISSUE REACTION TO RIBBON CATGUT AND PRESERVED OX FASCIA LATA STRIPS*

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IN A good many publications Koontz^{1, 2, 3, 4, 5} has pointed out the advantages of preserved ox fascia strips as suture material in various conditions. In 1932, he⁶ showed the differences in tissue reaction to catgut and kangaroo tendon as compared with ox fascia strips. The former are either soon absorbed or become friable and lose their tensile strength. Both catgut and kangaroo tendon cause a marked reaction in the tissues—with a wet wound, an abundant cellular reaction, and marked leukocytic infiltration. This is more marked in the case of kangaroo tendon than in that of catgut. On the other hand, preserved ox fascia lata strips show no tendency to be absorbed in the early months (eight months) that they have been studied, and there is no cellular reaction around them. There is, however, a reaction on the part of the surrounding fibrous tissue—new fibroblasts growing in among the implanted connective tissue fibrils of the ox fascia lata strips, becoming incorporated with them, and revivifying them by furnishing living cells and blood vessels which wander in between the old inert collagen fibrils.

In 1933, Lowsley and Bishop⁷ introduced the use of ribbon catgut for repairing nephrotomy wounds. The following year, Lowsley⁸ reported an operation for ptosis of the kidney, using the same material, and stated that the kidney stayed where it was placed. He has also used the material to plicate the bulbocavernosus and ischiocavernosus muscles for the surgical relief of impotence in man.^{9, 10} Lowsley has also used ribbon gut for the relief of urinary incontinence by placing an encircling band of it around the urethra.¹¹ Experiments in animals, in connection with this operation, showed that the ribbon gut had been replaced by scar tissue in autopsies done from three weeks to two months after operation. He has also used the material to plicate muscles in operations for the relief of incontinence of both urine and feces.¹² As a further use for the material, Lowsley has used it as a mattress suture to join the membranous urethra to the urinary bladder following total perineal prostatectomy.¹³

Hawes¹⁴ reports the use of ribbon gut in the repair of 26 herniae. However, as two of the 26 had very early recurrences (one in three weeks and one in eight months), and as all of the herniae, except one, were of a very simple type, his results cannot be considered remarkable. Strode¹⁵ has used ribbon gut for the control of hemorrhage in operations on horseshoe kidneys. Chanis¹⁶ has recently reported the use of the material in operations for the suspension of the uterus.

* Read before the American Surgical Association, Cleveland, Ohio, April 6-8, 1942.

All of the above-mentioned users of ribbon gut used chromic gut, and chromic gut was also used in the experiments reported herein.

Due to the known tendency of catgut to be absorbed (Lowsley states⁸ that the material used by him was absorbed after three weeks), we wondered if preserved fascia lata strips would not serve his purpose better than ribbon catgut. Probably one reason that he did not use it was that ribbon catgut can be made very much longer than it is possible to get lengths of ox fascia strips. The longest ox fascia strips obtainable are only about 12 inches long. However, the strips can be easily spliced, and in that manner made as long as necessary. Lowsley gives as one of the principal reasons for using ribbon gut the fact that it does not cut through. The same thing, of course, applies to fascia strips.

The excellent results obtained by Lowsley speak well for his skill as a surgeon, but one wonders if his results might not have been even better if he had used a suture material that was not only not absorbable, but had the same qualities as ribbon gut in not cutting through. Very likely, the ribbon gut, in a great many cases during the processes of absorption, was replaced by other fibrous tissue. This is what undoubtedly occurred when bands of ribbon gut were used to encircle the urethra. This process is not new, but is not constant enough to be reliable. Many years ago Lister,¹⁷ Marcy,¹⁸ and more recently Sir Charles Ballance¹⁹ observed the process of substitution and replacement in animal sutures (plain and chromicized catgut and peritoneal ox ligatures) by tissues of the host, so that the substituted tissues took the same form as the original suture. Everyone knows that this does not always occur, as in most instances, after a short time, no trace of the original animal suture can be found. Replacement similar to that mentioned above has also been shown experimentally in chromicized kangaroo tendon. In his experiments on this suture material, reported in 1932, Koontz⁶ used heavy kangaroo tendon to suture the sheath of the rectus muscle. Fourteen months later, in one instance, on casual observation it looked as if the original suture were still intact. However, on further investigation, it was found that the groove which the original suture had occupied in the sheath of the rectus was still present and filled with loose areolar tissue. Microscopic examination showed no trace of the original kangaroo tendon. In another similar case, the same condition was found four months after operation.

We believe that it will generally be agreed that in most cases such sutures as those mentioned in the preceding paragraph will be absorbed, and further that in the few cases in which there is some fibrous substitution from the tissues of the host, the fibrous tissues substituted do not have the tensile strength of the original suture. There are, of course, exceptions to all rules.

We conducted some experiments upon dogs in order to determine the differences in the tissue reaction to ribbon gut and ox fascia lata strips. All the experiments were similar. The rectus sheath and muscle were incised on each side and sutured in each instance on the right side with a running stitch of ribbon gut, and on the left side by a running stitch of preserved ox fascia lata. The following are some of the protocols:

PROTOCOLS

Experiment 1.—March 28, 1940. *Operation:* Implantation of ribbon gut and ox fascia lata. A right rectus incision was made. The rectus sheath and muscle were divided and sutured with ribbon catgut, continuous suture. The initial end of the suture was tied, while at the terminal end the gut was not tied, but fixed through the sheath of the rectus with fine black silk after making one lock-stitch. The subcutaneous tissue and skin were closed with medium black silk continuous.

A left rectus incision was then made. The rectus sheath and muscle were divided and sutured with preserved ox fascia lata.* The subcutaneous tissue and skin were closed with medium black silk continuous.

April 12, 1940: Dog died (15 days after operation). Had had distemper for last few days prior to death. On examining the operative site, there was an obvious bulging on the left side, which was fluctuant and contained fluid. On opening this, a good deal of bloody fluid ran out, and the subcutaneous tissues were edematous and contained oily bubbles. The ox fascia was intact and not macerated in any way, but there was maceration of the tissues into which it was sewed. It pulled out, therefore, rather easily. Opening the right side showed the subcutaneous tissue to be edematous also, but there was no fluid collection. Most of the ribbon gut had disappeared, and in places there were some pieces of it left, which appeared like tissue paper. The initial knot was still present. Smear from both wounds showed pus cells but no bacteria.

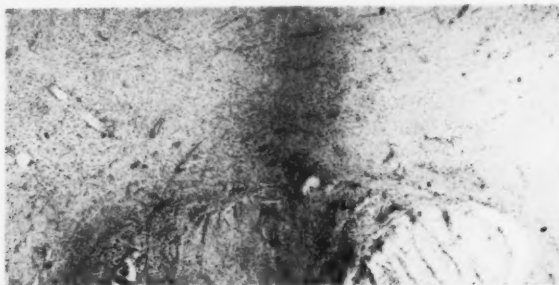


FIG. 1.—Photomicrograph showing organization of ox fascia lata with surrounding tissues. Four weeks after operation (Experiment 2). (X25)

Experiment 2.—April 4, 1940. *Operation:* Implantation of ribbon gut and ox fascia lata. The rectus sheath and muscle were divided on each side as before, and on the right side they were sutured with ribbon gut, continuous suture, the initial end being anchored in the same manner as the fascia lata instead of tied. The terminal end was fixed with a lock-stitch, reinforced with interrupted fine black silk sutures.

The left rectus was sutured in the usual manner with preserved ox fascia lata.

May 2, 1940: Dog killed (four weeks after operation). The sites of both operations were nicely healed without any evidence of infection or untoward reaction. The ox fascia lata was nicely healed in and organized with the surrounding tissue (Fig. 1). The ribbon gut was not absorbed and not organized at all with the other tissues, lying in place as an inert foreign body, and more or less friable (Fig. 2).

Experiment 4.—April 18, 1940. *Operation:* Implantation of ribbon gut and ox fascia lata. The implantation made just as in previous operations, except that the ox fascia lata was implanted first, in order to be sure not to contaminate it with preserving solution from the ribbon gut.

June 26, 1940: Dog killed (69 days after operation). None of the ribbon gut could be discovered except the knot at the upper end of the incision. This knot was removed for section (Fig. 3). The continuous suture of ox fascia lata was plainly visible on the left side, nicely healed in without untoward reaction.

Experiment 5.—May 2, 1940. *Operation:* Implantation of ribbon gut and ox fascia lata. The implantation made just as in Experiment 4, implanting the ox fascia lata first and the ribbon gut second.

* The material used in these experiments was all commercially prepared (Johnson and Johnson). The preserving fluid is 1 per cent biniodide of mercury in alcohol. Before using this material it should always be washed thoroughly in two successive basins of sterile salt solution, and then let stand in salt solution until ready for use. A good plan is to have the scrub nurse break the tubes and wash the fascia strips as soon as she is scrubbed up, so that they will have sufficient time to soak before the operator is ready for them.

TISSUE REACTION TO SUTURES



FIG. 2.—Photomicrograph of ribbon gut, four weeks after operation. No organization with surrounding tissues. Gut easily pulled out (Experiment 2). (X25)

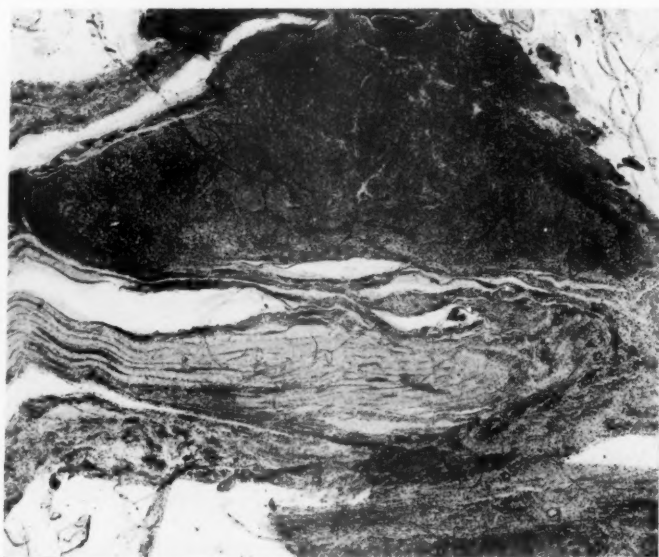


FIG. 3.—Section through ribbon gut. Sixty-nine days after operation. Gut surrounded by sterile abscess (Experiment 4). (X25)

June 26, 1940: Dog killed (55 days after operation). There was a stitch abscess on the right side which, however, did not penetrate below the subcutaneous tissue. No trace of the ribbon gut could be seen. On the left side, the continuous suture of ox fascia lata was plainly visible and nicely healed in.

Experiment 6.—May 9, 1940. *Operation:* Implantation of ribbon gut and ox fascia lata. The operation performed just as in Experiment 5, implanting the ox fascia on the left first, and then the ribbon gut on the right.

FIG. 4.

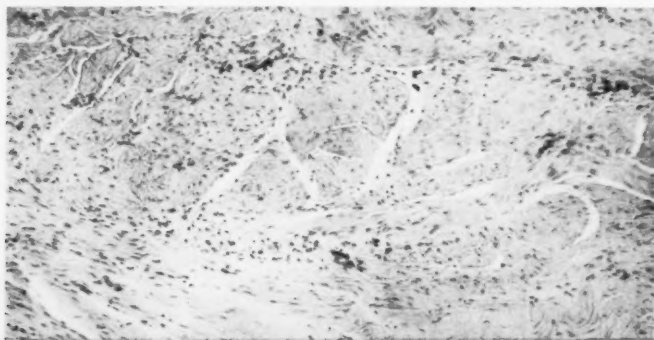


FIG. 5.

FIG. 4.—Photomicrograph of ox fascia lata. Three weeks after operation. Fibroblasts of host growing in between the collagen fibrils of the ox fascia lata (Experiment 6). ($\times 100$)

FIG. 5.—Photomicrograph of ribbon gut. Three weeks after operation. No organization, but gut encysted and surrounded by leukocytic reaction (Experiment 6). ($\times 25$)

May 30, 1940: Dog killed (three weeks after operation). Both sides were nicely healed. The ox fascia was well organized in with the other tissues (Fig. 4). Fibroblasts were found invading the fascia. In the case of the ribbon gut, all healing was complete, but there was no organization of the ribbon gut in with the other tissues. Cross-section showed it to be partially absorbed, but totally encysted, and it could be pulled out readily from the encysting tissues (Fig. 5).

The results obtained with the rubbon gut are, therefore, very similar to those obtained with ordinary catgut. This is what one would expect. Doubtless, the chemicals with which catgut is treated in preparation have something to do with its absorption. Also, it is heated in the process of preparation,

which alters the physical state of the collagen fibrils. No such chemical or physical alteration takes place in the collagen fibrils of the preserved fascia strips. Besides, the strips are soft and pliable, and lend themselves readily to the ingrowth of fibroblasts from the surrounding tissues, while catgut is so hardened that it would be impossible for fibroblasts from the surrounding tissues to grow into it, even if there were no question of a complicating physical and chemical alteration of the fibrous framework.

CONCLUSIONS

Strips of preserved ox fascia lata offer the same advantages as ribbon catgut as a suture material in not cutting through, while they present the additional advantages of not being absorbed, and, by virtue of the invasion of fibroblasts from surrounding tissues, persisting as living sutures with an apparently undiminished tensile strength.

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EFFECT OF ORCHIECTOMY AND IRRADIATION ON CANCER OF THE PROSTATE*

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THE RELATIONSHIP OF FUNCTION of certain endocrine glands to prostatic carcinoma was first demonstrated by Huggins and Hodges⁶ who showed that this cancer is frequently inhibited by eliminating the testicular androgens by bilateral orchiectomy or by neutralization of androgenic activity by estrogen administration; conversely, cancer of the prostate is activated by injection of androgens. Subsequently, the favorable action of estrogens in prostatic cancer was confirmed by Herbst³ who reported that estradiol and diethylstilbestrol—the estrogens used by Huggins and Hodges—are substances which “seem to relieve pain due to local prostatic malignant tissue and bony metastatic carcinoma.” Huggins, Stevens, and Hodges⁸ showed that prostatic carcinoma is an abnormal growth of cells resembling adult prostatic epithelium rather than tissue of a more primitive nature. These cancers responded to modifications of the androgenic hormonal status like adult prostatic epithelium such as the cystic hyperplasia of the prostate of senile dogs which increases and decreases in size and function corresponding to changes in the androgenic activity as was shown by Huggins and Clark.⁵

In line with the work cited is the observation of Munger⁹ who treated 11 patients with prostatic cancer by transurethral resection of the prostate, irradiation of the prostatic area (several mapped-out areas were treated until usually each had received 2,000 roentgen units) and irradiation of each testicle (500 r.). Munger stated: “A study of several cases treated by testicular irradiation with resection seems to indicate that slightly better results were obtained than in those cases treated by resection and roentgenotherapy exclusive of the testicular application.”

It is the purpose of the present paper to survey the course and the results of treatment by surgical excision of the testes alone, and evidence is presented that irradiation of the testes in two cases did not eliminate the interstitial issue of the testes.

MATERIAL.—In most instances after opening the tunica vaginalis, the testis was dissected away from the epididymis, followed by closure of the tunica and skin in layers, without drainage. This achieves cosmetic and psychological effects in that two masses of tissue remain in the scrotum.

During the last 30 months, 45 patients with advanced prostatic carcinoma accompanied by local infiltration or metastases have been treated in this clinic

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† This investigation was aided by a grant from the Committee for Research in Problems of Sex, the National Research Council.

ORCHIECTOMY FOR CANCER OF PROSTATE

by orchiectomy; 32 of these men had metastases demonstrable on roentgenologic examination of the bones; 21 patients were operated upon more than one year ago, and 15 men in this group had osseous metastases. Roentgenotherapy was employed in no case in this clinic.

RESULTS OF ORCHIECTOMY FOR PROSTATIC CANCER

In the entire series of 45 patients subjected to orchiectomy, there have been eight deaths, all in men with extensive metastases to bone (Table I).

FIG. 1.



FIG. 2.



FIG. 3.

FIG. 1.—(Hospital No. 62292) Adenocarcinoma of prostate with extensive metastases to pelvis; pre-operative roentgenogram.

FIG. 2.—(Hospital No. 62292) The same patient as in Figure 1, 201 days after orchiectomy.

FIG. 3.—(Hospital No. 62292) The same patient as in Figures 1 and 2, 467 days after orchiectomy, showing complete disappearance of the radiographic evidence of metastases.

In four of these men, carcinomatosis was the principal cause of death, while in the others it was of secondary importance. From a clinical standpoint, 31 men have had a sustained improvement lasting as long as 30 months; nine men have had a temporary improvement followed by recurrence of symptoms; and in five men there was no improvement following castration.

In 11 men of the group of 21 patients operated upon 12-30 months ago, there has been significant improvement; these patients are free from symp-

TABLE I
MORTALITY FOLLOWING ORCHIECTOMY FOR PROSTATIC CANCER

45 Patients Treated in 30 Months

	Initials	Hospital Unit No.	Age, Years	Weight of Testes		Histologic Nature of Neoplasm	Time Since Orchiectomy, Days	Apparent Cause of Death
				Gm.				
(1)...	F. F.	274090	70	18	18	Adenocarcinoma	4	Pulmonary embolism
(2)...	J. W. G.	26645	67	10	10.3	...	9	Pulmonary embolism
(3)...	C. R.	49318	74	18	20.6	Undifferentiated carcinoma	10	Pneumonia. Pyogenic arthritis of knee
(4)...	O. A.	252777	75	12.7	18.1	Adenocarcinoma	53	Cerebral apoplexy
(5)...	S. R.	241797	72	0.7	10.2	Undifferentiated carcinoma	193	Lobarpneumonia. Carcinomatosis
(6)...	G. P.	246583	73	9.0	8.2	Undifferentiated carcinoma	234	Carcinomatosis
(7)...	P. M.	256818	56	13.4	17.0	Undifferentiated carcinoma	332	Carcinomatosis
(8)...	M. M.	247587	57	8.6	7.8	...	500	Carcinomatosis



FIG. 4.—M. C. (a patient of Dr. W. S. Grant). Metastatic adenocarcinoma of the prostate in inguinal nodes on the left; the same region 107 days after orchietomy is shown on the right

toms, acid and alkaline phosphatase values of serum are in or near the normal range, there has been complete or partial resolution of roentgenographic evidence of osseous metastases, and a great decrease in size and in the stony consistency of the primary neoplasm on rectal examination. In four patients, extensive osseous metastases have completely disappeared, as determined roentgenographically (Figs. 1, 2 and 3).

Thus, it is clear that there are many failures in the treatment of prostatic cancer by orchietomy.

THE "FAILURE CASES" FOLLOWING ORCHIECTOMY FOR PROSTATIC CANCER

The following observations were made in those patients in whom orchietomy did not produce marked resolution of the neoplasm or in whom clinical improvement was not long sustained.

(1) *The Histologic Nature of the Tumor.*—Sections of the prostate gland were studied in 16 patients and it was found that a correlation could be made

with the clinical course following orchiectomy. Cytologically, the tumors were classified into two groups: (a) Adenocarcinoma where the tumor formed acini (Fig. 5). All of these tumors were in Grades II or III. (b) Undifferentiated carcinoma where tubular structure was not fabricated but the tumor presented solid masses of malignant cells (Fig. 7). The clinical course following orchiectomy could be related easily to the cellular pattern. Without exception the tumor was undifferentiated in all of those patients who died from carcinoma, while it was adenocarcinoma in those patients whose course was satisfactory (Figs. 4-6). Classification of the tumors into adenocarcinoma and undifferentiated carcinoma, therefore, seems to have meaning although the types interdigitate. Both undifferentiated carcinoma and adenocarcinoma contained large amounts of acid phosphatase and are regarded as

FIG. 5.

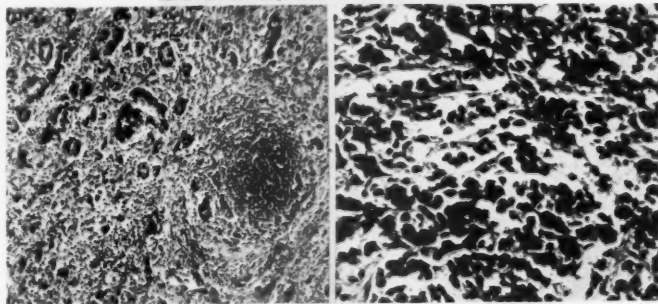
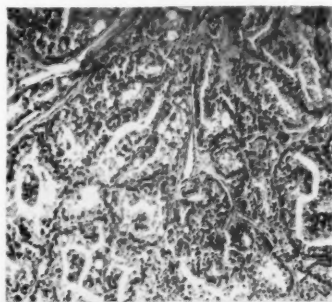


FIG. 6.

FIG. 7.

FIG. 5.—M. C. Metastatic prostatic adenocarcinoma, Grade II, in inguinal lymph node, before orchiectomy.

FIG. 6.—M. C. An inguinal lymph node 107 days following bilateral orchiectomy. There has been a marked decrease in the size of the acini which contain little or no secretion, and an increase of connective tissue stroma. There are areas of connective tissue scarring containing slits occupied by pyknotic and fused cellular nuclei.

FIG. 7.—Undifferentiated carcinoma of the prostate, stained by the method of Gomori for acid phosphatase.

cancers of adult prostatic epithelium, since the formation of large amounts of acid phosphatase in the prostate is a secondary sex characteristic of a chemical nature. For purposes of prognosis, it is impossible to distinguish between them by studying the serum phosphatases since both may cause elevation of acid phosphatase when they have metastasized.

(2) *The Size of the Testis.*—Three of the patients who died of carcinoma had testes which, considered singly, weighed 8–10 Gm. at operation. The smallness of the testis is due to a decrease of germinal epithelium, although sheets of Leydig cells remain. The presence of testes, markedly lighter than the normal weight of about 20 Gm., is a bad prognostic sign. Atrophy of germinal epithelium with real or apparent hypertrophy of the interstitial cells is not confined to prostatic cancer. Sand and Okkels¹⁰ observed grave destruction of tubular epithelium in 24 instances in 72 cases of men dying from accidental causes or sterilized by law.

(3) *Decrease of the Primary Neoplasm when the Metastases are Producing a Fatal Carcinomatosis.*—It was observed in certain of the failure cases that the primary tumor greatly decreased in size while the metastases were advancing to produce serious illness, such as spinal cord compression (two cases) or even fatal carcinomatosis. This strange phenomenon, in which the hard, and more or less enlarged, prostate gland—at times greatly enlarged—underwent a decrease in size and hardness so that the prostate was completely soft and very small, was observed five times in the presence of the advancing neoplastic process elsewhere in the body. It appears that in certain patients the site of prostatic cancer in bone marrow or lymph nodes as metastasis is more favorable than the original prostatic location; it is possible that adjacent macrophages may facilitate separation of essential foodstuffs, such as androgens, from the body fluids for the improved nutrition of the cancerous metastases.

In other patients in the failure group, slight or no decrease in size of the primary neoplasm occurred, and here the prognosis is bad. Therefore, in advanced prostatic cancer when the primary tumor has undergone marked atrophy, one cannot say merely from atrophy of the primary tumor, as determined by local examination, that the course of the disease is favorable.

(4) *Supplemented Estrogen Administration in Postcastration Failure.*—It was shown by Huggins and Clark⁵ that in dogs estrogen administration in adequate dosage masks the stimulating effect on the prostate of injected androgens; it was further demonstrated in this laboratory^{6,7} that estrogen has a beneficial effect at times in prostatic cancer. Accordingly diethylstilbestrol, 1–3 mg. daily by mouth, was administered to ten patients with advanced prostatic cancer, who had an unsatisfactory response to castration. In one patient, there was a slight reduction of serum acid phosphatase but not to the normal range.⁷ In nine patients, the disease was not perceptibly influenced. It seems that estrogen is able to neutralize to some extent the physiologic properties of the testis androgens, such as testosterone, but not to neutralize the effect of the adrenal androgens. It is believed that estrogen does not usefully supplement orchiectomy in prostatic cancer.

(5) *Hot Flashes: A Favorable Prognostic Sign.*—The presence of severe hot flashes was seen in all of the cases favorably influenced by orchiectomy, but also in certain of the unfavorable cases. These vasomotor incidents are not believed to be of therapeutic importance but are taken as a sign of androgen-

estrogen deficiency and are usually of favorable prognostic importance. There is no contraindication to their suppression with small doses of estrogen as described by Huggins, Stevens, and Hodges.⁸

THE EFFECT OF IRRADIATION OF THE TESTES IN ADVANCED PROSTATIC CANCER

Data were obtained on two patients in whom roentgenotherapy was applied both to the pelvis and testes. The clinical course following irradiation was similar in each.

CASE REPORTS

Case 1.—Hospital No. 269674: F. M., age 47, complained of perineal pain radiating into the right leg, and rectal examination disclosed a large indurated cancer of the prostate, which on biopsy was found to be an adenocarcinoma, Grade II. Four months after the onset of symptoms irradiation was applied to the pelvis over 55 days, according to the following formula: 800 KV; 10 Ma.; Filtration, 1 Mm. Pb; 1.56 Mm. Sn; 2.62 Mm. Cu; 3 Mm. Al; portals 15×20 cm.; tube distance 70 cm.; F.S.D. 250 roentgen units; duration of each treatment 7.5 minutes; ten treatments each to anterior and posterior right hip region and ten treatments each to anterior and posterior pelvis. There was symptomatic relief for two months when symptoms recurred and a second series of treatments were given through a 20×30 cm. portal; eight treatments to anterior and seven to posterior pelvis; the testes were not screened during the second course of treatments. Relief of symptoms occurred for about six weeks.

Eighty-seven days following the completion of therapy the original symptoms had returned and the patient used canes for walking. On rectal examination, the prostate was nodular, greatly enlarged and of stony consistency; a roentgenogram showed osteoplastic metastases in the right side of the pelvis. Orchiectomy was then performed; the testes weighed 15.7 and 16.3 Gm.

Case 2.—H. J. (ref. by Dr. C. C. Moore, Pittsburgh), age 63, complained of pain in the lower back and in the right leg; clinical and biopsy examinations of the prostate gland revealed carcinoma, and there was roentgenographic evidence of metastases in the spine. Roentgenotherapy was administered as follows: In a seven-day period, he received a total dosage of 1,600 roentgen units to each of four portals cross-firing the prostate gland given at the rate of 200 r. to each of two anterior portals daily with fields 16×19 cm. in size (200 K.V. constant potential; 0.5 Mm. Cu, 2 Mm. Al. Filtration added). The testes were protected in the usual way with lead rubber but undoubtedly received "back-scattering" of radiation in this series. A second irradiation was given six months later, without lead rubber protection, and the patient received 1,000 roentgen units measured in air, to each of four portals using a field 18×21 cm. in size with the application of 100–200 r. daily without screening of the testes. The patient failed to improve from this regimen and the prostate gland remained hard and nodular, so that bilateral orchiectomy was performed three months later. The operation was followed by a relief of symptoms and decrease in the size and consistency of the prostate gland.

The testes in each case presented similar cytologic characteristics, namely, profound atrophy of the germinal epithelium with preservation of Sertoli cells and apparent or real hyperplasia of the Leydig cells (Fig. 8).

The histologic appearance of the testis following irradiation in man corresponds to data obtained in experimental animals. Bourg¹ in the immature rat found that 1,000 roentgen units destroyed the seminiferous epithelium, but left interstitial cells intact. Heald, Beard, and Lyons² found in rats that an irradiation dosage of 1,152–4,608 roentgen units left the Leydig cells in a functional condition. Hu and Frazier⁴ subjected rabbits to a series of ex-

posures to roentgen ray, aggregating 2,268 roentgen units (4.4 erythema skin doses) over a period of 15 days and produced complete atrophy of the germinal epithelium without interference with the secretory functions of the testes.

It is thus apparent that roentgen ray irradiation, in the amounts stated, is ineffective in destroying the secretory function of the testes and is inadequate as a therapeutic agent in prostatic cancer in man.

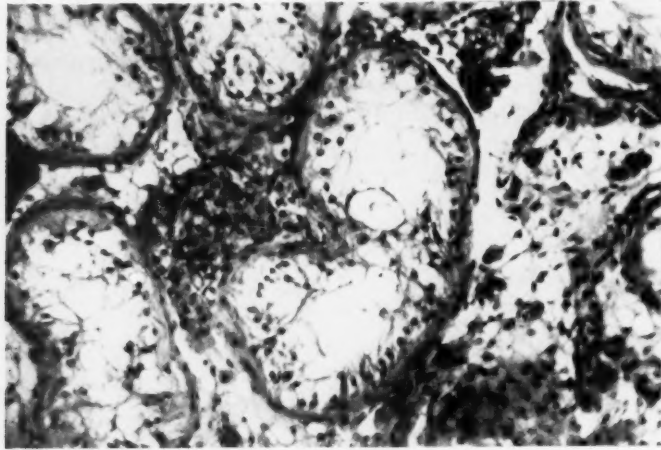


FIG. 8.—F. M. (Hospital No. 269679). Histologic appearance of the testis 87 days following completion of extensive irradiation with roentgen ray. The dosage is described in the text. Note tubular atrophy with preservation of interstitial cells.

SUMMARY AND CONCLUSIONS

In a series of 45 consecutive patients with advanced prostatic cancer, in whom the primary treatment was bilateral orchiectomy, there were eight deaths, all in men with metastasis to bones; in four of these, carcinomatosis was the principal cause of death. In five men, castration caused no clinical improvement; in nine patients there was temporary improvement, and in 31 cases a sustained inhibition of the disease occurred, lasting at least as long as 30 months.

The tumors were classified according to their cytologic appearance into two groups: adenocarcinoma and undifferentiated carcinoma. All of the deaths from carcinomatosis and the patients with no or slight improvement after orchiectomy had undifferentiated carcinoma, while in the more satisfactory cases the cytologic appearance was adenocarcinoma. The findings of testes much lighter than the usual weight of 20 Gm. signified a poor prognosis.

A phenomenon of interest, in which a great decrease occurred in the size of the primary neoplasm, while the metastases were advancing, was observed five times in this series.

Estrogen administration was not found to be a useful supplement in the failure cases after orchiectomy.

Roentgen irradiation of the testes in the doses stated, produced atrophy of

the germinal epithelium, but not of the interstitial cells of the testis, and is inadequate as a therapeutic agent in human prostatic cancer.

DISCUSSION.—DR. EVARTS A. GRAHAM (St. Louis, Mo.): I rise only because Doctor Phemister asked me to stick my neck out. I do not know anything about the prostate, of course, but I do want to say that I am delighted to have this work presented here. I have been hearing about it. I think it is the sort of presentation that the American Surgical Association needs more of.

The apology which I made, in getting to my feet, about the fact that I knew nothing about the prostate was meant to emphasize another point about this Association. The Association, up until a few years ago, was degenerating, may I say, into an organization which had only so-called general surgeons in it. I do not know whether you can degenerate into a general surgeon or not. At about that time it was felt desirable that the membership of the Association be leavened somewhat by adding to it some of those men who had gone off into specialties of various kinds. Now some of us who went off into thoracic surgery already had our membership in this Association, so nothing could be done about us. But an attempt was made to add new life to the Association by adding such people as Doctor Huggins, and I think the fact that that was done has been amply justified by his splendid presentation to-day.

I think this has another very important bearing, and that is, to my mind, it represents an approach to the subject, to the problem of cancer which is of interest, of course, to so-called general surgeons the same as to anyone else. We are particularly fortunate in having a paper of this sort, dealing with the subject of cancer in a broad aspect like this.

There are one or two specific points to which I would like to refer. Doctor Huggins did not have time to go into the historic aspects of this question, but castration for cancer of the prostate is a very old idea. If I am not mistaken, I think Bland-Sutton advocated it in the eighties, but it was given up, and it has been taken up since then by others and dropped after one or two experiences.

It was partly on the basis of the early results obtained in cancer of the prostate after orchietomy that the effort was made to treat cancer of the breast by removal of the ovaries, and the same sort of thing has happened again, namely, that after a little experience it has been dropped. But there have been sufficiently interesting results accumulated to make this approach at least one of great interest to the study of certain types of cancer.

Of course, Doctor Huggins has carried the procedure very much farther by applying new knowledge, new fundamental knowledge about cancer of the prostate and about the acid and alkaline phosphates to the rationality of the idea of orchietomy. But all in all, from every possible point of view from which one regards this work, one can only commend it to the highest degree.

DR. ALFRED BLALOCK (Baltimore, Md.): As a member of the Program Committee, I would like to express our appreciation for this paper and comment on one or two things Doctor Graham has said.

In the first place, Doctor Huggins was a general surgeon, who later developed a particular interest in genito-urinary surgery. But the main thing I want to say is this, that he demonstrates in this work, I think, the value of a prepared mind. Doctor Graham made the comment that the testicles were removed in a few instances many years ago for this lesion, but Doctor Huggins came across this because of the fundamental nature of his work in other fields. Many of you know of the notable contributions he has made to the study of bone. It was because of that information that he was able to grasp the significance of these findings on acid phosphates and to apply them to the treatment of this disease.

Having visited in Doctor Phemister's clinic, and having seen Doctor Huggins' cases, I can tell those of you who have not seen them that I am sure you will be perfectly amazed.

As Doctor Graham has said, if a real contribution is made in cancer in any one field, such as Doctor Huggins has made, at least, it raises our hopes of being able to find out something about cancer in other parts of the body.

I think that we as an Association should be very happy in having this excellent work presented here.

DR. WILLIAM JASON MIXTER (Boston, Mass.): I simply wish to say that we have had one such case at the Massachusetts General Hospital that I know of, treated in this way, a case of carcinoma of the prostate with metastasis to the spine, and with very severe pain, that I operated upon for cord compression. Roentgenotherapy did not work very well, and orchiectomy seems to have done a very good piece of work.

DR. CHARLES HUGGINS (closing): I am highly flattered, and very much embarrassed, by the kind remarks of Doctor Graham and Doctor Blalock. I would like to make just a few comments on the matter of the history of orchiectomy for carcinoma of the prostate. I believe the only person who, knowingly, operated to remove the testes for carcinoma of the prostate was Dr. Hugh Young, who did this in two patients, with negative results. It is unfortunate that his cases apparently were not of that type which responds well.

The wave of operations that has been mentioned for removal of the testes for prostatic conditions, I believe, has been confined otherwise to benign prostatic hypertrophy.

With regard to the breast, I am on very uncertain grounds, because I think it is extremely unwise to carry over data from one cancer to another cancer. We do know that in the case of the breast this structure is affected by two hormones, one estrogen, from the ovary, the other, prolactin from the pituitary. If it is a prolactin tumor, then ovariectomy would obviously be a suitable procedure. I think we have fallen into one error lately, and that is to treat patients who are still menstruating, with cancer of the breast, by roentgenotherapy of the ovaries. Certainly, it is impossible to eliminate the interstitial cells of the breast by roentgenotherapy of the ovaries, and I think it is extremely likely that the bad results that are obtained in the breast cancer, at the present time, by attempting to modify the endocrine state, are due to the use of roentgen ray. I strongly feel that surgical ovariectomy should be performed in patients with advanced cancer of the breast, with metastasis, who are in the menstrual age rather than irradiation.

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